ABSTRACTS OF WORLD MEDICINE

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Pathology

454. **Further Studies of the Minute Structure of Collagen Fibrils.** (Neuere Ergebnisse zum Feinbau der kollagenen Fibrille)
E. KUHNKE. *Zeitschrift für Rheumaforschung* [*Z. Rheumaforsch.*] **17**, 259–274, Aug., 1958. 11 figs., bibliography.

At the Institute of Physiology, University of Bonn, the author has studied the minute architecture of tendon, using a thin-slice technique suitable for electron microscopy. Evidence is presented that at 640 Å. the regularly spaced cross-striations of collagen fibrils occur at the periphery of the fibril. They can be partly removed by suitable cutting or by the action of hyaluronidase; this enzyme, in contrast to proteolytic enzymes, attacks the intact surface of the fibril and can thus produce depolymerization of the whole fibril. Experiments are described in which some of these fibres were subjected to heat and traction. The results suggested that the individual fibrils lie in an amorphous interfibrillar substance to form, in the living state, a three-dimensional meshwork, such an arrangement making for flexibility. The author concludes, however, that much remains to be discovered regarding the minute structure of the collagen fibril. [This is an interesting, speculative paper.]

G. Loewi

455. **The Occurrence of the Sex Chromatin in White Blood Cells of Young Adults. I. Study of Normal Peripheral Blood**
M. S. N. MURTHY and E. VON HAAM. *American Journal of Clinical Pathology* [*Amer. J. clin. Path.*] **30**, 216–223, Sept., 1958. 6 figs., 8 refs.

In this study, carried out at Ohio State University College of Medicine, Columbus, examination of 400 leucocytes in stained smears of peripheral blood from each of 50 healthy young students (25 males and 25 females) for the presence of sex chromatin showed that in the women the average incidence of typical " drumsticks " was 6·5% (range 2 to 17·8%). No typical drumsticks were observed in the leucocytes of the men, but the occurrence of small clubs, which were not unlike drumsticks, was recorded in 4·08% (range 0·8 to 9·9%), a definitely higher proportion than in the female subjects. The authors remark that " it is tempting to suggest that these might be the male counterpart of the drumsticks in the women ".

Many non-segmented and a few segmented neutrophil leucocytes from the women showed a plano-convex, deeply basophilic, well outlined mass of chromatin closely applied to the inner aspect of the nuclear membranes, as first described by Barr *et al.* (*Anat. Rec.*, 1950, **107**, 283); viewed end on, this structure was seen to be elliptical in shape. The examination of blood smears from 3 women in whom the incidence of drumsticks was low showed that the peripheral mass of sex chromatin described above was present in 12·3% of all polymorphonuclear leucocytes. It was notable that no drumsticks or other nuclear appendages were found in the few segmented polymorphonuclear leucocytes that contained the plano-convex or elliptical mass of sex chromatin.

From the results of this study, which confirms and supplements that of Davidson and Smith (*Brit. med. J.*, 1954, **2**, 6; *Abstr. Wld Med.*, 1955, **17**, 6), the authors concur that there are definite male and female patterns of sex chromatin. They stress the importance of avoiding distortion of the drumsticks and nuclei, which is best achieved by making the blood smear neither too thick nor too thin. Of the various procedures employed in the preparation of the smears of peripheral blood, air-drying and Wright's stain were found to give the most satisfactory results.

J. B. Wilson

EXPERIMENTAL PATHOLOGY

456. **The Polysaccharide Behaviour of Cancer Antigens**
J. G. MAKARI. *British Medical Journal* [*Brit. med. J.*] **2**, 355–358, Aug. 9, 1958. 17 refs.

The immunologically active substances detected in the serum and tissues of patients with cancer by the Schultz–Dale method, as previously described by the author (*Brit. med. J.*, 1955, **2**, 1291; *Abstr. Wld Med.*, 1956, **19**, 417), have been demonstrated in studies here reported from Muhlenberg Hospital, Plainfield, New Jersey, to behave like polysaccharides. In the separation of these substances from cancer and normal tissue antigens two procedures were followed: (1) precipitation with *iso*-propyl alcohol and deproteinization with chloroform and butyl alcohol, and (2) heating at 100° C. for 30 minutes with one-tenth volume of 2N sodium hydroxide, followed by dialysis and removal of extraneous matter by chloroform extraction.

The sensitizing substances thus obtained were shown by the Schultz–Dale test to behave as polysaccharides, being non-dialysable, resistant to boiling and to alkalis, and giving a positive reaction with the Molisch test. It is considered that the specific immunological activity of cancer antigens resides in these polysaccharide-like substances. The author adds that although these results

are preliminary in nature, the finding that cancer antigens are of a polysaccharide nature and the fact that polysaccharides are less complex to study immunochemically than are proteins give some "reason for optimism in our attempts to understand the cancer problem and a greater hope of its solution". *L. A. Elson*

457. **Detection of Antigens in Sera of Patients with Neoplastic Disease by Schultz–Dale Test. Its Possible Use as a Screening Procedure for Tumours**
J. G. MAKARI. *British Medical Journal* [*Brit. med. J.*] **2**, 358–361, Aug. 9, 1958. 4 refs.

In this further study [see Abstract 456] the possibility of modifying the Schultz–Dale test for detecting specific carcinoma antigen so that it could be used as a screening test for types of tumour other than carcinoma has been investigated. In the present study the sediment obtained by centrifugation of the carcinoma suspension at speeds between 3,000 and 10,000 r.p.m. was used for immunization of the guinea-pigs instead of that obtained by centrifugation at between 3,200 and 4,000 r.p.m., as in previous studies.

The results obtained with this method in the study of 566 specimens of serum from individuals and 704 from a blood bank are reported. A correct diagnosis was made in 89% of 262 cases of carcinoma, 73% of 130 cases of malignant tumour other than carcinoma, and 94% of 35 cases of benign tumour. Further, a positive response was obtained in 77·9% of 59 cases of precancerous lesions and suspected tumour, whereas such a response was observed in only 12·5% of 80 healthy blood donors and 12·6% of 704 specimens of normal serum from the blood bank.

It is considered that this modification would be useful as a tumour-screening procedure, while the author's original method would serve as a specific diagnostic test for carcinoma. *L. A. Elson*

458. **Hypertensive Vascular Disease as a Consequence of Increased Arterial Pressure. Quantitative Study in Rats with Hydralazine-treated Renal Hypertension**
G. M. C. MASSON, L. J. MCCORMACK, H. P. DUSTAN, and A. C. CORCORAN. *American Journal of Pathology* [*Amer. J. Path.*] **34**, 817–833, Sept.–Oct., 1958. 12 figs., 19 refs.

An experimental investigation of the effect on hypertensive vascular disease of the prevention and remission of renal hypertension is reported from the Cleveland Clinic Foundation, Cleveland, Ohio. In rats unilateral nephrectomy was carried out and partial renal infarction induced by tying the remaining posterior renal artery. Following this procedure there was a progressive rise in blood pressure over 5 to 7 days, and the animals uniformly developed severe and acute vascular lesions. Rats given hydrallazine in drinking water did not become hypertensive, and those given hydrallazine from the 7th day promptly became normotensive again.

In the hypertensive group the small arterioles of the heart, mesentery, and pancreas showed subendothelial oedema and thickened, irregular walls surrounded by fibrin-like exudate which gave a positive periodic-acid–Schiff reaction and stained dark blue with phosphotungstic-acid–haematoxylin. In rats treated with hydrallazine from the time of operation the changes were much fewer and less intense; in rats so treated from the 7th to 15th days the lesions were predominantly fibrous. The lesion in animals given hydrallazine after hypertension had continued for one month showed healing and perivascular scarring, while the lesions in animals treated for one month and surviving during a subsequent month of hypertension corresponded to those seen in the untreated hypertensive group. In 4 out of 10 rats given hydrallazine continuously and showing only mild hypertensive lesions in other sites there was unexpected renal vascular damage involving the large arterioles and arteries, demonstrating the sensitivity of the renal vascular bed to hypertension.

The findings, in the authors' view, indicate that the maintenance of normal blood pressure with hypotensive drugs prevents the onset of hypertensive extrarenal vascular lesions and thus lend support to the thesis that the occurrence of vascular lesions is in great part a consequence of increased blood pressure. *H. Caplan*

459. **The Effect of Tobacco Tar on the Bronchial Mucosa of Dogs**
E. E. ROCKEY, M. KUSCHNER, A. I. KOSAK, and E. MAYER. *Cancer* [*Cancer (Philad.)*] **11**, 466–472, May–June, 1958. 8 figs., 7 refs.

In experiments on a group of 7 dogs tobacco tar was applied directly to the bronchial mucosa through a surgically formed tracheo-cutaneous fistula 3 to 5 times a week for periods up to 11 months. Serial biopsy showed that squamous metaplasia was rapidly induced, and at necropsy this change was found not to be limited to the area of direct application in dogs treated for long periods. No signs of precancerous lesions were found, however, in any of the animals. *G. Calcutt*

460. **The Cocarcinogenic Activity of Cigarette Tobacco Tar**
A. GELLHORN. *Cancer Research* [*Cancer Res.*] **18**, 510–517, June, 1958. 1 fig., 16 refs.

The carcinogenic activity of cigarette tobacco tar was studied at the College of Physicians and Surgeons, Columbia University, New York, in a series of experiments carried out on mice. Tar obtained by combustion of cigarette tobacco at 500° to 700° F. (260° to 371·1° C.) in a specially designed smoking machine was not carcinogenic when applied dissolved in acetone or benzene to the skin of mice 5 or 6 times a week. Using a similar procedure the author found that benzpyrene with tobacco tar and benzpyrene with the cocarcinogenic agent croton oil produced a significantly greater proportion of papillomata and carcinomata than did benzpyrene alone. The rate of development of carcinomata in groups of mice with papillomata receiving benzpyrene and tobacco tar was significantly higher than in mice treated with benzpyrene alone or with benzpyrene and croton oil, suggesting that tobacco tar has a cocarcinogenic effect or otherwise promotes the development of epitheliomata in mice given a threshold dose of benzpyrene.

The author refers to " the difficulty of translating animal studies to the human subject ", and concludes that the findings in this investigation " can only be considered as circumstantial evidence to support the concept that air pollution " by a variety of known carcinogens, including benzpyrene " together with cigarette smoke inhalation, could reasonably explain the higher incidence of bronchogenic carcinoma in city dwellers compared with those living in rural communities ".

L. A. Elson

461. **A Correlated Histological, Cytological, and Cytochemical Study of the Tracheobronchial Tree and Lungs of Mice Exposed to Cigarette Smoke. I. Bronchitis with Atypical Epithelial Changes in Mice Exposed to Cigarette Smoke**

C. LEUCHTENBERGER, R. LEUCHTENBERGER, and P. F. DOOLIN. *Cancer* [*Cancer (Philad.)*] **11**, 490–506, May–June, 1958. 29 figs., 23 refs.

In experiments performed at Western Reserve University, Cleveland, Ohio, 23 mice were exposed intermittently to cigarette smoke for periods of 17 to 300 days, the histopathological findings in the major bronchi being then correlated with the histochemical findings and compared with those in control animals Most of the experimental animals developed bronchitis. The findings in their bronchi were of three types: (1) no significant change, (2) bronchitis with mild epithelial changes and a possible slight increase in nucleolar deoxyribonucleic acid (DNA) content, and (3) bronchitis with pronounced proliferative changes, often atypical and in many respects similar to carcinoma *in situ*, together with an increased nucleolar DNA content. One or more of these features might be present in different parts of the same bronchus. In contrast, none of the control animals developed bronchitis and no atypical changes were found in their bronchial epithelium.

G. Calcutt

462. **On the Healing of Experimental Ulcers of the Large Intestine after Disruption of Its Innervation.** (О заживлении экспериментальных язв толстого кишенника при нарушении его иннервации)

N. I. SOMINSKIJ. *Архив Патологии* [*Arh. Patol.*] **20**, 17–22, No. 9, 1958. 5 figs., 13 refs.

It is well known that, clinically, ulcers of the large intestine often show considerable delay in healing in spite of medical treatment. In an attempt to elucidate this problem ulcers of the colon were produced in 24 cats by introducing a rubber tube containing 3 large perforations into the colon via the rectum for a distance of about 12 cm. and inserting in the tube a swab soaked in strong acetic acid. The 3 ulcers thus produced took from 5 to 10 days to heal; this period could be reduced by medicinal treatment and physiotherapy. In some of the animals, however, it was shown that if, before inducing ulceration, the solar plexus was injured by diathermy the healing of the ulcers was delayed for up to 2 to 3½ months, and in one case perforation occurred. The importance of trophic influences and therefore of intact innervation of the intestine in the healing of ulcers is stressed.

A. Swan

CHEMICAL PATHOLOGY

463. **Serum Enzymes in Disease. I. Lactic Dehydrogenase and Glutamic Oxalacetic Transaminase in Carcinoma**

M. WEST and H. J. ZIMMERMAN. *A.M.A. Archives of Internal Medicine* [*A.M.A. Arch. intern. Med.*] **102**, 103–114, July, 1958. 13 figs., 25 refs.

At the Chicago Medical School and the University of Illinois College of Medicine the serum levels of lactic dehydrogenase (L.D.) and glutamic oxalacetic transaminase (G.O.T.) were estimated in 173 patients with carcinoma or sarcoma, the object being to correlate, if possible, the values obtained with the type of neoplasm, the presence or absence of metastases, and the results of liver function tests. The serum L.D. level was raised on one or more occasions in 76 of the patients, generally in association with hepatic metastases. The serum G.O.T. level was raised in 53 out of 121 patients in whom this was determined; in all except one of these the high level was closely associated with hepatic or myocardial metastases.

H. Harris

464. **Serum Enzymes in Disease. II. Lactic Dehydrogenase and Glutamic Oxalacetic Transaminase in Anemia**

H. J. ZIMMERMAN, M. WEST, and P. HELLER. *A.M.A. Archives of Internal Medicine* [*A.M.A. Arch. intern. Med.*] **102**, 115–123, July, 1958. 9 figs., 22 refs.

The serum levels of lactic dehydrogenase (L.D.) and glutamic oxalacetic transaminase (G.O.T.) were determined in 82 patients with various forms of anaemia. The serum L.D. level was raised in all patients with megaloblastic anaemia and sickle-cell anaemia and in some with sickle-cell haemoglobin-C disease and sickle-cell thalassaemia. There was no increase in this level in patients with anaemia due to chronic or acute haemorrhage, infection, or bone-marrow hypoplasia. The serum G.O.T. level was raised only when there was also evidence of hepatic disease.

H. Harris

465. **Normal and Pathologic Proteins and Flocculation Tests. A Contribution to the Study of the Mechanism of Flocculation Tests**

R. ARMAS-CRUZ, G. LOBO-PARGA, M. MADRID, and C. VELASCO. *Gastroenterology* [*Gastroenterology*] **35**, 298–308, Sept., 1958. 26 refs.

In this paper from the Hospital San Juan de Dios, Santiago, Chile, the authors discuss the mechanism of serum flocculation reactions, and especially their dependence upon the protein fractions of the serum. Such reactions have been used for many years for various purposes, but they have been applied to the diagnosis of jaundice only since 1938, when Hanger introduced the cephalin–cholesterol test. The results of this test and of others of a similar nature such as the colloidal gold, thymol turbidity, and colloidal red tests are consistently positive, in the authors' experience, in cirrhosis, hepatitis, and other instances of hepatocellular jaundice and almost always negative in jaundice due to canalicular obstruction. However, these reactions are not specific

since they depend upon non-specific alterations in the equilibrium of the serum proteins—particularly a decrease in the albumin fraction and an increase in the γ-globulin fraction—and positive results are frequently obtained in disseminated lupus erythematosus, subacute bacterial endocarditis, and rheumatoid arthritis.

Gray (*Proc. Soc. exp. Biol.* (*N.Y.*), 1942, **51**, 400), using pure protein fractions isolated from the serum by electrophoresis, has demonstrated the flocculating activity of γ globulin and the antagonistic action of albumin in the colloidal gold reaction, while other authors have obtained similar results with the cephalin–cholesterol test. Electrophoretic analysis of the serum in the acute stage of infective hepatitis shows a significant reduction in albumin content and a corresponding increase in globulin content, and the present authors have studied the question whether flocculation is simply the result of this reduction in the albumin:globulin ratio or whether qualitative changes in the proteins also occur. To this end pure albumin and γ globulin were separated from the serum of normal subjects and patients suffering from hepatitis, cirrhosis, obstructive jaundice, lupus erythematosus, rheumatoid arthritis, and subacute bacterial endocarditis. The fractions obtained from patients with similar diseases were pooled and their activity in various flocculation reactions were studied quantitatively and compared.

Analysis of the results obtained (which are set out in a number of tables) showed that a positive result was due not only to a decrease in the albumin:globulin ratio, but also to an increase in the flocculating activity of the γ globulin and a decrease in the protective power of the albumin (which was generally less marked in cirrhosis than in other diseases giving a positive reaction). Of the tests in general use, the cephalin–cholesterol test was found to be the most resistant to the inhibitory effect of albumin on flocculation. On the other hand in both the thymol turbidity test and the distilled water test of Cabello *et al.* (*Rev. méd. Chile*, 1949, **77**, 24), although albumin inhibited the precipitation produced by γ globulin, it was unable to prevent turbidity. The colloidal gold, colloidal red, and colloidal blue tests were strictly parallel in behaviour. *E. Forrai*

466. **The Investigation of Symptomless Glycosuria with the Galactose and Cortisone Modified Glucose Tolerance Tests**

R. B. Goudie, W. P. Stamm, and S. Dische. *Journal of Clinical Pathology* [*J. clin. Path.*] **11**, 428–436, Sept., 1958. 1 fig., 16 refs.

At the Royal Air Force Institute of Pathology and Tropical Medicine, Halton, Bucks, glucose tolerance and galactose tolerance tests were carried out on 65 patients with a history of glycosuria. Of these 65 patients, 11 were referred because the results of previous glucose tolerance tests were equivocal, while 54 were referred either for investigation of glycosuria found during routine examination or because they complained of symptoms suggestive of diabetes mellitus.

The difficulty of assessing the significance of the glucose tolerance curve in symptomless glycosuria is discussed. It is suggested that in the presence of a normal fasting blood glucose level both the peak and the 2-hour blood glucose level should be used in assessing the tolerance. A galactose tolerance curve is considered to be of value because the peak here gives some indication of what the rate of absorption of glucose would be in the glucose tolerance test. Thus a high peak in the glucose tolerance test is more likely to indicate impaired tolerance if the galactose tolerance curve is normal.

A cortisone-modified glucose tolerance test was performed on 27 patients with glycosuria, but it was found to be of little help in diagnosis. *H. Harris*

467. **Improved Accuracy of Tes-tape in Estimating Concentrations of Urinary Glucose**

H. S. Seltzer and M. J. Loveall. *Journal of the American Medical Association* [*J. Amer. med. Ass.*] **167**, 1826–1830, Aug. 9, 1958. 2 figs., 13 refs.

"Tes-tape" is an indicator paper strip used to test urine for the presence of glucose. The paper is impregnated with an enzyme, glucose oxidase, which acts on β-D-glucose in the presence of oxygen to liberate hydrogen peroxide, which in turn oxidizes *ortho*tolidine, also present in the paper, to a blue pigment. Since the amount of pigment formed is directly related to the concentration of glucose present, a quantitative estimation can be made by comparison with a standard colour chart, but in some cases the test has been found to give an erroneously low reading. Improvements in manufacture have recently been made which, it is claimed, have increased the accuracy of the test for quantitative purposes, and the present authors have carried out a reassessment of its reliability. They point out that errors of assessment may have arisen in the past from the use of standard solutions made up by dissolving anhydrous glucose, which is primarily α-D-glucose, in sugar-free urine, whereas for a positive reaction with tes-tape it is essential that glucose be present in the β-form. Moreover, since oxygen must be available for completion of the reaction, a low reading will be obtained if the paper remains immersed in the urine instead of being dipped and then exposed to air.

The accuracy of tes-tape was assessed both with standard solutions of glucose in urine and with diabetic urine of known glucose content. More than 3,000 separate estimations were made with various batches of tes-tape. In both cases interpretation of the colour reaction after the standard one-minute interval gave highly reliable results at glucose concentrations of 0·5% (3+) or less, but was seriously inadequate at glucose concentrations of 2% (4+) or more. By allowing an additional minute for maximum colour development, however, the accuracy of the test at high concentrations was considerably improved.

The authors recommend that in using tes-tape the strip should be laid flat against a white background before reading, and also that if the one-minute reading is 0·5% (3+) or more a final reading should be made after 2 minutes. Used in this way tes-tape provides a convenient and reliable method for the semiquantitative estimation of urinary glucose. *Victor M. Rosenoer*

HAEMATOLOGY

468. **Inhibition of Leukocyte Agglutination by Serum from Patients with Systemic Lupus Erythematosus: a Manifestation of the L.E. Cell Phenomenon**
S. L. LEE. *Blood* [*Blood*] **13**, 778–788, Aug., 1958. 2 figs., 18 refs.

The author observed that the tendency of leucocytes suspended in normal serum to undergo spontaneous agglutination owing to cell death, lysis, and formation of nucleoprotein " clot " was accelerated in the presence of quinacrine hydrochloride (final concentration 0·2 to 0·4 mg. per ml.), and was invariably complete after 3 hours' incubation at 37° C., but that agglutination failed to occur in the presence of serum containing the lupus erythematosus (L.E.) factor. In this report from the Mount Sinai Hospital, New York, he discusses the various factors influencing this leucocyte agglutination inhibition (L.A.I.) and its value in diagnosis. That the lack of agglutination in the presence of L.E. serum was due to the presence of an inhibitory factor rather than to the absence of an agglutinating factor was suggested by the fact that the ability to inhibit agglutination could be conferred on normal serum by the addition of a small volume (about 6%) of L.E. serum. Leucocyte agglutination did occur in the absence of quinacrine, but was delayed. Normal serum seemed to be essential for leucocyte agglutination, which was absent or unsatisfactory in solutions of sodium chloride, albumin, and gamma globulin. Examination by the phase-contrast microscope of leucocyte suspensions in normal serum showed that before agglutination began many cells " exploded " and the nuclei of these lysed cells stretched into fibrous strands to enmesh the intact cells.

When leucocytes were incubated with L.E. serum in the presence of quinacrine, smears from the sediment showed swelling and homogenization of all nuclei, with the production of L.E. bodies, but phagocytosis to produce L.E. cells did not occur. Control preparations using L.E. serum without quinacrine showed that most cell nuclei retained their normal structure, but rosette formation and some L.E. cells were easily demonstrable. Leucocyte agglutination was inhibited in the presence of deoxyribonuclease, but the nuclear changes differed from those seen in the presence of L.E. serum; further, although the addition of sodium oxalate reversed the inhibition caused by deoxyribonuclease (by removing magnesium ions) it did not affect the inhibition due to L.E. serum. Inhibition of leucocyte agglutination could not be demonstrated when platelet-poor L.E. plasma was substituted for L.E. serum.

Parallel L.A.I. and L.E.-cell tests were performed on 1,183 specimens of blood. The L.E.-cell reaction was positive in 68% and the L.A.I. reaction in 59% of 164 specimens from 34 patients with clinical systemic lupus erythematosus, and in only one instance was the L.A.I. reaction positive when the L.E.-cell reaction was negative. In similar studies carried out on 1,019 specimens of blood from cases of other diseases the L.A.I. reaction was positive in 12 cases, but the L.E.-cell reaction in none. The author suggests that both L.E. serum and deoxyribonuclease interfere with leucocyte agglutination by altering deoxyribonucleoprotein, though in different ways. Although the L.A.I. test is simple to perform, it is less specific than the L.E.-cell test, and it is inadequate as a primary test for systemic lupus erythematosus.

M. Wilkinson

469. **Complement Fixation Reaction with DNA and Leukocyte Material in Systemic Lupus Erythematosus. Correlation with the L.E. Cell Phenomenon and the Clinical Status**
C. M. PEARSON, C. G. CRADDOCK, and N. S. SIMMONS. *Journal of Laboratory and Clinical Medicine* [*J. Lab. clin. Med.*] **52**, 580–587, Oct., 1958. 1 fig., 8 refs.

Recent work has shown that complement-fixing reactions occur between a constituent of the serum γ-globulin fraction of some patients with systemic lupus erythematosus (possibly identical with the L.E.-cell factor) and cell nuclei, nucleoprotein, or deoxyribonucleic acid (DNA). This paper from the University of California School of Medicine, Los Angeles, describes the results of such complement-fixation tests on sera from patients with systemic lupus erythematosus and other diseases and correlates them with the occurrence of the L.E.-cell phenomenon. Tests were performed in parallel with DNA prepared from normal human spleen and with nuclear material from lysed human leucocytes as the " antigens ".

Of 20 sera from patients with systemic lupus erythematosus, 7 gave a positive complement-fixation reaction with DNA, while 5 out of 16 gave a positive reaction with leucocyte material. In no case were the results discordant. Positive complement-fixation reactions occurred only with sera from patients with severe or moderately severe disease, usually giving a strongly positive L.E.-cell reaction. The result was negative in all cases in which the disease was only mildly active and in 3 in which it was more severe. In one case a positive complement-fixation reaction with leucocyte material was obtained before the reaction with DNA and the L.E.-cell reaction became positive. The authors suggest that this finding supports the hypothesis that a separate serum factor is responsible for each of the 3 reactions.

Complement-fixation tests were carried out with the same " antigens " on sera from 38 patients with various rheumatic and collagen diseases and from 15 with miscellaneous non-rheumatic diseases. In all cases the results were negative.

M. Wilkinson

470. **On the Interaction of Dead Leukocytic Nuclei, L.E. Factor and Living Leukocytes in the L.E. Cell Phenomenon**
D. J. NATHAN and I. SNAPPER. *Blood* [*Blood*] **13**, 883–893, Sept., 1958. 6 figs., 12 refs.

In this paper from the Beth-El Hospital, Brooklyn, New York, the authors report some further studies on the mechanism of L.E.-cell formation. Bare leucocyte nuclei were prepared by incubating normal human leucocytes with 0·2% citric acid solution for 30 minutes at 37° C. The nuclei were then washed with normal saline and incubated with serum from patients with dissemin-

ated lupus erythematosus (L.E. serum) for one hour. After rewashing they were incubated for 2 hours with a fresh preparation of buffy coat from the same normal human donor and then examined for L.E. cells. In each of 10 experiments with 2 potent L.E. sera abundant L.E. cells were seen, whereas in 10 control experiments with normal sera no L.E. cells were found. In all instances the supernatant L.E. serum showed a marked reduction or total loss of L.E.-factor activity after contact with the bare nuclei. This confirms the finding of Miescher and Fauconnet (*Experientia* (*Basel*), 1954, **10**, 252) that the L.E. factor is adsorbed by isolated leucocyte nuclei.

To determine whether intact leucocytes would adsorb the L.E. factor the authors used a suspension of washed normal leucocytes which had been kept at room temperature for 24 hours. These leucocytes were mostly dead but intact, and after incubation with potent L.E. serum only a few L.E. cells resulted. The leucocytes were then separated from the serum by centrifugation and, after further washing, were incubated with fresh normal buffy coat for 2 hours. In none of the 5 experiments performed was there any further increase in the number of L.E. cells, nor was there any reduction in the L.E.-cell activity of the L.E. serum after its separation from the leucocytes.

These findings seem to support Miescher's opinion that the L.E. factor is an antinuclear auto-antibody with no affinity for the chemically different cytoplasmic nucleic acid. It would appear that viable leucocytes may play some role in L.E.-cell formation in addition to that of phagocytosis, since the bare nuclei did not undergo the swelling and homogenization characteristic of the L.E. phenomenon when they adsorbed L.E. factor, but only when viable leucocytes were subsequently added. The authors suggest that the cytoplasm of the dead leucocyte acts as a barrier between the L.E. factor and the nuclear material which must be breached by viable leucocytes before the L.E. factor can be adsorbed to the nucleus, and that the living leucocytes serve the additional function of transforming nuclei to which L.E. factor has been adsorbed into swollen, homogeneous L.E. bodies.

M. Wilkinson

471. **Non-Addisonian Megaloblastic Anemia. The Intermediate Megaloblast in the Differential Diagnosis of Pernicious and Related Anemias**

H. FUDENBERG and S. ESTREN. *American Journal of Medicine* [*Amer. J. Med.*] **25**, 198–209, Aug., 1958. 4 figs., bibliography.

The features which distinguish Addisonian pernicious anaemia from other forms of megaloblastic anaemia are discussed. It is pointed out that in non-Addisonian megaloblastic anaemia the erythrocyte precursors in the bone marrow may often be distinguished from those seen in classic pernicious anaemia; for these erythrocyte precursors the authors use the term intermediate megaloblasts. They are smaller and more compact than classic megaloblasts, have a slightly coarser nuclear pattern, and do not show the asynchrony between nuclear maturation and haemoglobinization in cytoplasm which is characteristic of the true megaloblast. The diagnostic value of the recognition of these intermediate megaloblasts is illustrated by reference to 4 cases seen at Mount Sinai Hospital, New York, of which 3 were instances of non-Addisonian megaloblastic anaemia and one was an example of classic pernicious anaemia superimposed on thalassaemia minor.

It is suggested that the occurrence of intermediate megaloblasts may depend on the existence of an abnormality of iron metabolism in addition to deficiency of folic acid or vitamin B_{12} (cyanocobalamin). In some cases of non-Addisonian megaloblastic anaemia this disturbance of iron metabolism may be a simple deficiency syndrome, as in cases of malabsorption or gross dietary deficiency; in other cases the defect may be principally one of utilization, as in chronic infections and carcinomatosis.

A. G. Baikie

MORBID ANATOMY AND CYTOLOGY

472. **The Thyroid Gland after Treatment of Hyperthyroidism by Partial Thyroidectomy or Iodine^{131}**

R. C. CURRAN, H. ECKERT, and G. M. WILSON. *Journal of Pathology and Bacteriology* [*J. Path. Bact.*] **76**, 541–560, 1958. 29 refs.

The histological changes have been studied in the thyroid gland after treatment of thyrotoxicosis by surgery (7 cases) and with I^{131} (13 cases). In the remnant of the thyroid left after partial thyroidectomy from 1 to 16 years after operation, cellular hyperplasia decreases and colloid storage increases with lengthening time after operation Six patients died within 74 days of therapy with I^{131}. Radioactive iodine was detected in these glands and the acute effects of irradiation were seen in these cases. The chief features are nuclear pyknosis and cellular necrosis, breakdown of follicles and the development of bizarre cell forms, thrombosis of capillaries and small blood-vessels and oedema of the stroma. The distribution of I^{131} in the autoradiographs and the injury to tissues are patchily distributed.

Chronic radiation effects were seen in 7 cases studied at longer intervals, up to 5½ years, after I^{131} treatment. Many abnormal cell forms persist. There is widespread and severe derangement of the follicles, which are mainly small and irregular. There is little storage of colloid. Many small blood-vessels are telangiectatic. Lymphocytic infiltration is rare, but there is extensive fibrosis, often perifollicular, and stromal oedema is often notable.

The histological features are discussed in relation to the functional changes in the thyroid after surgery and after irradiation.—[Authors' summary.]

473. **Pathologic Findings in Benign Pulmonary Histoplasmosis. Preliminary Report**

H. C. SWEANY, D. GORELICK, F. C. COLLER, and J. L. JONES. *Diseases of the Chest* [*Dis. Chest.*] **34**, 119–137, Aug., 1958, and 257–273, Sept., 1958. 45 figs., 18 refs.

In this paper from the Missouri State Sanatorium, Mt. Vernon, the authors discuss the histological techniques available for demonstrating the presence of *Histoplasma capsulatum* and report their findings in lung tissue

obtained from 37 cases of proved histoplasmosis. Of the 37 patients, 2 had circumscribed lesions (" inactive disease ") and 16 had clinically active disease. The histological appearances in these cases were compared with those in specimens of lung tissue from 24 patients suspected of having histoplasmosis but who were later proved to be suffering from another disease, usually tuberculosis. In addition, material from 4 patients with both tuberculosis and histoplasmosis and from 3 who were known to have sarcoidosis was examined. Gomori's methenamine silver stain was found to be the most satisfactory. Culture or inoculation into animals was effective in 50% of cases only and the results of the complement-fixation test were erratic. The histological features in a number of typical cases are described in some detail, 8 histological groups being recognized as follows: (1) a lesion seen as a " coin " shadow on the radiograph due to a single central focus with centrifugal spread; (2) a similar single lesion, but consisting of encapsulated infiltrates with a larger, earlier focus of infection; (3) nodular lesions; (4) chronic pneumonitis; (5) ulcerative lesions; (6) bronchiectasis; (7) pleuritic involvement; and (8) mixed types. *P. Mestitz*

474. **The Morbid Anatomy of Early Tuberculous Infiltration and Its Further Development as Seen in Lungs Resected at Operation.** (К вопросу о патологической анатомии раннего туберкулезного инфильтрата и формы его прогрессирования в легких, иссеченных при хирургических вмешательствах)
Е. S. RASKINA. *Архив Патологии* [*Arh. Patol.*] **20**, 45–50, No. 7, 1958. 2 figs., 5 refs.

The results are reported from the Leningrad Tuberculosis Research Institute of the examination of specimens of lungs resected at operation from 99 patients with pulmonary tuberculosis whose history, clinical and radiological, testified to the presence, at one time, of " an early tuberculous infiltrate with tissue breakdown, or changes developing therefrom ".

The lesions found were of five types. (1) Large caseous masses (tuberculomata) up to 6 cm. in diameter, with varying degrees of encapsulation (11 cases). Chemotherapy proved ineffective in all of these cases, and pneumothorax was tried in 8 without benefit. (2) Single " giant " cavities (more than 5 cm. in diameter), with or without bronchogenic dissemination (31 cases). In half of these cases the disease became manifest clinically only after cavitation had occurred. Most of the patients had received large doses of streptomycin, isoniazid, and PAS in various combinations, but collapse therapy had not been tried as a rule before operation. (3) Multiple cavities, usually one large one and several smaller ones, surrounded by numerous, scattered, non-cavernous foci (11 cases). These patients had also been mostly treated by chemotherapy without collapse therapy. (4) Single small cavities surrounded by numerous encapsulated caseous foci 0·1 to 0·5 cm. in diameter (40 cases). In 27 of these patients the disease had been diagnosed only after the appearance of clinical or radiological evidence of tissue breakdown. Pneumothorax was ineffective in the 23 cases in which it was tried. (5) Multiple small cavities interspersed with numerous encapsulated caseous foci (6 cases). In this group also pneumothorax had proved ineffective. The lesions of Types 2, 3, 4, and 5 all belong to the category of fibro-caseous tuberculosis. Descriptions of the histology of each type are given [but contain nothing unexpected]. *A. Swan*

475. **Pathological Study of Lung Tissue Removed at Operation from Cases of Primary Tuberculosis.** (Examen anatomique des pièces de résection réalisée au cours de la primo-infection)
P. GIRAUD, H. METRAS, P. LAVAL, H. PAYAN, H. GIRAUD, and M. GRÉGOIRE. *Pédiatrie* [*Pédiatrie*] **13**, 483–491, 1958. 4 figs., 11 refs.

The authors present, from the Clinique Médicale Infantile, Marseilles, the results of a morbid anatomical study of specimens of lung or lymph nodes removed at operation in 54 cases of primary tuberculosis, this number representing some 5% of all cases of primary tuberculosis admitted during the period of the study. Only the hilar nodes were removed in cases without obvious parenchymal involvement, the indications in these cases being bronchial obstruction or the formation of a bronchial fistula.

Typical caseous and sometimes liquefied tissue was found. The parenchymal lung lesions were more varied. The primary focus was often included in the specimen. Cavities and lesions indistinguishable from those of post-primary tuberculosis were seen. In one case a large cavity was found to be sterile as a result of previous antituberculous chemotherapy. Involvement of the bronchi in the tuberculous lesion was a major pathological finding. True tuberculous bronchiolitis as well as bronchiolitis obliterans was found, in addition to frank bronchiectasis. Occasionally dense caseous foci were found in the lung tissue in cases which showed radiological consolidation, but which gave rise to no clinical symptoms. No case of obstructive emphysema was seen, but secondary bacillary infections were very common.

The authors were impressed by the fact that many of the lesions demonstrated were apparently irreversible, yet clinically they were often silent. Nevertheless, if not resected these lesions would have constituted a constant threat of post-primary tuberculosis. It is emphasized that these severe lesions were found in only some 5% of primary infections (as stated above). The authors suggest that in these cases removal of the caseous lymph nodes may save the lung parenchyma from damage, and that removal of functionless lung segments may save further trouble from progressive tuberculosis.
John Lorber

476. **Squamous Metaplasia of the Respiratory Tract Epithelium. An Autopsy Study of 214 Cases. 3. Relation to Disease.** [In English]
K. SANDERUD. *Acta pathologica et microbiologica Scandinavica* [*Acta path. microbiol. scand.*] **44**, 21–32, 1958. 2 figs., 34 refs.

The significance of squamous epithelial metaplasia in relation to local respiratory-tract disease and to diseases outside the respiratory system was studied at the Gade

Institute, University of Bergen, Norway. Extensive metaplasia was particularly frequent in myocardial infarction, a condition in which, as in metaplasia of bronchial epithelium, tobacco smoking is considered to play a part. In cases of acute and chronic pulmonary disease the incidence of metaplasia was only slightly higher than normal, but in chronic renal disease with uraemia squamous metaplasia of the respiratory-tract epithelium was surprisingly frequent, being present in 29 of the 30 cases of uraemia studied. The author suggests that the reason for this may lie in the well-known tendency of patients with uraemia to develop bronchial infections and that the metaplasia occurs after the local destruction of the normal epithelium by infection. He points out, however, that since in most cases several different factors, especially terminal bronchopneumonia, may be present, the precise significance of each factor in the development of squamous epithelial metaplasia is difficult to determine. *J. B. Wilson*

477. **The Systemic Lesions of Whipple's Disease**
P. FARNAN. *Journal of Clinical Pathology* [*J. clin. Path.*] **11**, 382–390, Sept., 1958. 7 figs., 44 refs.

In this report from St. George's Hospital, London, a description is given of the principal pathological findings in 7 fatal cases of intestinal lipodystrophy (Whipple's disease), together with the main necropsy findings in 60 additional cases reported in the literature. The commonest finding was of material staining positive by the periodic-acid–Schiff technique within macrophages in the jejunal mucosa and in mesenteric lymph nodes; such macrophages were widely distributed in many cases, being found, for example, in other lymph nodes, in serous membranes, and in the endocardium. Marked loss of subcutaneous fat and skin pigmentation were also very common, while rather less frequent were serous effusions and fibrous thickening of serous membranes. Endocardial vegetations occurred in about one-third of the 67 cases reviewed. Histochemically, the Schiff-positive material was shown to react like a mucopolysaccharide.

The author suggests that the fundamental defect in Whipple's disease is an alteration in the ground substance of the jejunal mucosa; he describes his (unsuccessful) attempt to reproduce similar pathological changes in 6 mice and 5 rabbits by the parenteral injection of a 2% solution of hog's gastric mucin.

A. Wynn Williams

478. **Cutaneous Petechiae in Fatal Coronary Artery Disease**
L. M. GERLIS. *Journal of Clinical Pathology* [*J. clin. Path.*] **11**, 391–395, Sept., 1958. 4 figs., 18 refs.

The author describes from the Grimsby General Hospital a rare sign in cases of death due to acute coronary insufficiency which has not apparently been previously mentioned in the literature. It takes the form of cutaneous petechiae which appear at sites commonly associated with the referred pain of cardiac origin; it was observed in 8 cases, of which 5 were from a personally studied series of 360 deaths due to coronary insufficiency (an incidence of 1·7%) where a search for petechiae was specifically made. These petechiae, it is suggested, may be caused by intense efferent stimuli along a sympathetic nerve pathway, similar to that involved in referred pain, possibly by the agonal relaxation of blood vessels previously damaged by prolonged spasm. It is also suggested that the cutaneous reflexes may be accompanied by equally violent spasm of the coronary arteries. In 4 of the present cases there were haemorrhages directly related to the coronary arteries themselves and in 3 of these there was involvement of surrounding nerves. It is concluded that the sign provides useful supporting post-mortem evidence of acute coronary arterial insufficiency, particularly when these arteries themselves show no recent organic lesion. *A. Wynn Williams*

479. **The Gastric Mucosa in Pernicious Anaemia: Biopsy Studies.**
A. WYNN WILLIAMS, N. F. COGHILL, and F. EDWARDS. *British Journal of Haematology* [*Brit. J. Haemat.*] **4**, 457–464, Oct., 1958. 4 figs., 37 refs.

An account is given of the histological findings in 44 patients with pernicious anaemia on whom gastric biopsy was performed. Mucosal atrophy, usually complete, was always present and a moderate degree of infiltration with inflammatory cells was common, occurring in at least half the patients. Parietal cells were sometimes seen in the mucosa. In fact, the histological appearances were frequently indistinguishable from those seen in other patients without pernicious anaemia. There was no important correlation between the clinical and histological findings. Our results are compared with those of other observers and it is concluded that there are no pathognomonic lesions in the gastric mucosa in this condition.—[Authors' summary.]

480. **Infarcts of the Pancreas**
J. W. MCKAY, A. H. BAGGENSTOSS, and E. E. WOLLAEGER. *Gastroenterology* [*Gastroenterology*] **35**, 256–264, Sept., 1958. 5 figs., 17 refs.

A total of 41 cases of pancreatic infarct (defined as "tissue which had become necrotic because of impairment of its blood supply") were found among the records of 21,481 consecutive necropsies performed at the Mayo Clinic during the years 1924–55, an incidence of one in 523 or 0·19%. Infarction of the pancreas was most commonly found in association with conditions characterized by occlusive lesions of the arteries, such as periarteritis nodosa (15 cases), chronic nephritis (2 cases), and malignant hypertension (12 cases), which together accounted for 71% of the series. Embolic conditions made up a further 9%, and in the remaining 20% (8 cases) there had been terminal shock or congestive heart failure which may have been a contributory factor in the production of infarction. In no case was acute necrotizing haemorrhagic pancreatitis observed, which would seem to indicate that the latter is rarely caused by pancreatic infarction.

The gross and microscopic appearances are described and illustrated, and an attempt is made to correlate the findings with the clinical features, the conclusion being

reached that " it seems probable that in some instances, pancreatic infarcts may produce significant clinical symptoms ". In none of the 3 cases in which the symptoms were most characteristic of a pancreatic lesion, however, was any abnormality of serum enzyme activity found. *E. Forrai*

481. **The Lesions of Rheumatic Fever in Patients Treated with Cortisone. I. Special Consideration of Endomyocarditis.** (Las lesiones de la fiebre reumática en los enfermos tratados con cortisona. I. Consideración especial de la endomiocarditis)

I. COSTERO, R. BARROSO-MOGUEL, A. CHÉVEZ, G. MONROY, and R. CONTRERAS. *Archivos del Instituto de cardiología de México* [*Arch. Inst. Cardiol. Méx.*] **28**, 155–173, March–April [received July], 1958. 19 figs.

This report (the first of three) from the National Institute of Cardiology, Mexico City, describes the necropsy findings with particular reference to the cardiac lesions in 30 patients who died of rheumatic fever after treatment mainly with various compounds of cortisone. Vegetations on the cardiac valves were found in 24 (80%) of the cases. The principal histological differences between cortisone-treated patients and others were that the former showed: (1) a decrease in the number of Aschoff bodies and an increase in the number of fibroblasts and amount of collagen and scar formation; (2) slower organization of the fibrinoid substance of the vegetations, with a fibroblastic reaction in the adjacent tissues and absence of inflammatory cells; (3) a lessened tendency to organization and resorption of areas of necrosis. *M. Lubran*

482. **The State of the Renal Blood Vessels in Rheumatism. (A Comparison of Histological and Angiographic Appearances).** (Состояние сосудов почек при ревматизме (Гисто-ангиорентгенографические параллели))

V. V. SEROV. *Архив Патологии* [*Arh. Patol.*] **20**, 27–33, No. 7, 1958. 8 figs., 32 refs.

Histo-stereoangiographic methods were used [at the Sečenov Medical Institute, Moscow] in a post-mortem study of the kidneys of 25 patients aged 14 to 60 years who had died of rheumatic heart disease with decompensation and of 25 control subjects, including healthy persons who had died suddenly as a result of trauma. In rheumatism pronounced changes are present in the renal vessels which have a definite relationship to the phase of the rheumatic process. In acute exacerbations of rheumatic fever widespread inflammatory changes with increased vascular permeability are found, mainly in the small arteries in the renal cortex, while during periods of quiescence sclerotic changes are prevalent in the same vessels. The degree of vascular change in the kidneys is directly related to the duration of the disease and the number of acute attacks.

The inflammatory and sclerotic changes in the renal blood vessels which are characteristic of this disease bring about a disturbance of blood flow in part of the renal circulation. A number of compensatory adaptive mechanisms can be demonstrated, mainly consisting in arterio-venous anastomoses and pyramidal collateral vessels. These vessels allow a certain amount of blood to by-pass the cortical circulation, a fact which may play some part in the development of renal disturbances and of cardiovascular insufficiency in patients who have rheumatic heart disease.—[From the editorial summary.]

[The technical details of the method of investigation are not given, and the contrast medium used is not specified. The bibliography is poor, the latest reference from the foreign literature being dated 1938, and the author gives no indication of any acquaintance with Trueta's work or its further development by others. In itself, however, his work appears to be sound.]

A. Swan.

483. **Subcutaneous Nodules of Still's Disease**

E. G. L. BYWATERS, L. E. GLYNN, and A. ZELDIS. *Annals of the Rheumatic Diseases* [*Ann. rheum. Dis.*] **17**, 278–285, Sept., 1958. 9 figs., 8 refs.

The histological appearances of the subcutaneous nodules in rheumatic fever and rheumatoid arthritis are sufficiently defined and characteristic to enable a satisfactory differentiation to be made on the grounds of morbid anatomy alone. This paper from the Postgraduate Medical School of London describes a study in which the histological features of subcutaneous nodules in 57 cases of rheumatic fever and 22 cases of adult rheumatoid arthritis were compared with those in 12 cases of juvenile rheumatoid arthritis (Still's disease), defined as having its onset before the age of 17 years.

The nodules from the patients with Still's disease resembled, and in most instances were indistinguishable from, those from the patients with rheumatic fever, showing the same absence of necrosis and palisading, and the presence of oedema, well marked vascular islands, and a fibrinoid lattice. There was, however, a higher incidence of fibrosis and this was greater in amount than in rheumatic-fever nodules, although not so great as in the nodules of adult rheumatoid arthritis. Of the 12 cases, only one, in a boy aged 13, was diagnosed histologically as rheumatoid arthritis, though the nodules in a second case showed palisading. Of the 22 cases of adult rheumatoid arthritis, the nodules in 20 showed a typical histological picture of the disease, while of the larger group of 57 cases of rheumatic fever, in only one were the histological appearances suggestive of rheumatoid arthritis. Within the group of cases of Still's disease no correlation was found between the histological features and the patient's age, time since onset, erythrocyte sedimentation rate, or the Rose–Waaler test result. The significance of the findings is discussed. A review of 197 cases of Still's disease showed that pyrexia, rash, splenomegaly, and pericarditis occurred with greater frequency than in 75 cases of adult rheumatoid arthritis, while on the other hand a positive Rose–Waaler reaction and the presence of nodules were less frequent in Still's disease. It is considered probable that the differing manifestations in these two age groups are mainly due to the changes in the host with age.

[The paper is well illustrated with photomicrographs of the histological lesions.] *Harry Coke*

Microbiology and Parasitology

484 (a). **The Isolation, Characteristics, and Nomenclature of the Infective Agent *Leptospira monjakow*.** (История открытия, характеристика и номенклатура возбудителя лептоспироза *L. monjakow*)
A. A. VARFOLOMEEVA. *Журнал Микробиологии, Эпидемиологии и Иммунобиологии* [*Ž. Mikrobiol. (Mosk.)*] **29**, 36–42, No. 8, Aug., 1958. 3 figs., 15 refs.

484 (b). **The Serology of *Leptospira pomona* and *L. icterohaemorrhagiae*.** (О серологических типах лептоспир—*L. pomona L. icterohaemorrhagiae*)
V. V. ANAN'IN. *Журнал Микробиологии, Эпидемиологии и Иммунобиологии* [*Ž. Mikrobiol. (Mosk.)*] **29**, 42–45, No. 8, Aug., 1958.

484 (c). **The Identity of *Leptospira* Types DV-V and *L. pomona*.** (Об идентичности видов лептоспир ДВ-В и *L. pomona*)
V. S. KIKTENKO, V. V. ANAN'IN, and N. I. KAŠANOVA. *Журнал Микробиологии, Эпидемиологии и Иммунобиологии* [*Ž. Mikrobiol. (Mosk.)*] **29**, 46–49, No. 8, Aug., 1958. 7 refs.

In 1937 Terskih isolated from the blood of a patient with " water fever " a species of *Leptospira*, apparently peculiar to the U.S.S.R., which he named *L. monjakow*. During the next few years similar organisms were isolated in the U.S.S.R. from cattle, horses, pigs, field mice, rats, and other animals which were all subsequently shown to be identical with *L. monjakow*, and it became recognized that a febrile infection due to this organism, in which meningism occurs frequently and jaundice only rarely, occurs in all parts of European and Asiatic Russia.

At first the study of this species was confined to the U.S.S.R., but in 1954 a strain was sent to Kmety of Bratislava, who stated that *L. monjakow* was identical with *L. pomona*. To check this claim antisera were prepared against 4 type strains of *L. monjakow* and 10 of *L. pomona* and used in cross-agglutination reactions and cross-protection experiments in rabbits, the results of which showed that the two organisms are indeed identical.

It is therefore recommended that the name *L. monjakow* be abandoned in favour of *L. pomona*. Similar experiments have shown that the Far Eastern Type-A leptospira, first isolated by Tarasov *et al.* in 1938 and described by Kiktenko and Anan'in in 1940, is identical with *L. mitis*, described by Johnson in 1942, and it is suggested that, on grounds of priority, this organism should be renamed *L. tarasovi*. *K. Zinneman*

485. **Neutralization of Common Cold Agents in Volunteers by Pooled Human Globulin**
G. G. JACKSON, H. F. DOWLING, and T. O. ANDERSON. *Science* [*Science*] **128**, 27–28, July 4, 1958. 8 refs.

This paper reports the demonstration in human gamma globulin of protective antibodies against the common cold. Nasal secretions were obtained from two persons with characteristic common colds, filtered to remove bacteria, tested in tissue culture and in mice to ensure the absence of known viruses, and their infectivity then demonstrated by instillation, diluted 1 in 100, into the nostrils of volunteers, who developed an acute coryzal illness. Four matched groups of student nurses, selected at random, were then given, by nasal instillation, one or other of the two specimens of infectious secretion diluted with: (A) Hanks solution; (B) boiled human globulin concentrated to ±12 g. protein per 100 ml.; (C) human serum albumin; and (D) pooled human globulin in a final concentration of ±8 g. protein per 100 ml. respectively. In each instance one part of a 1:10 dilution of secretion was incubated at 37° C. for 30 minutes with 9 parts of the test diluent and 0·2 ml. of the resulting dilution used for nasal instillation.

Of the 65 nurses in Group A and the 20 in Group B, 34 (52%) and 11 (55%) respectively developed colds. In Group C the incidence was only slightly less, 8 (44·5%) out of 18 nurses developing colds. Of the 59 nurses in Group D, however, colds were observed in only 6 (10%). Colds developed in none of 12 control subjects who were given instillations of gamma globulin only, and in 9 (18%) of 49 who were given Hanks solution only. The gamma globulin delayed the onset of symptoms among those members of Group D who were not entirely protected, and all the individual symptoms of the common cold were modified in these subjects. *Joyce Wright*

486. **A Further Study of the Kveim Reaction in Sarcoidosis and Tuberculosis**
H. L. ISRAEL, M. SONES, H. BEERMAN, and T. PASTRAS. *New England Journal of Medicine* [*New Engl. J. Med.*] **259**, 365–369, Aug. 21, 1958. 9 refs.

The Kviem test was performed on 46 patients attending the Henry Phipps Institute, University of Pennsylvania, with sarcoidosis and on 29 in-patients at the Philadelphia General Hospital with tuberculosis. The material used was prepared from a large number of lymph nodes excised from a single patient with sarcoidosis, the method of preparation being described. The reaction was negative in all the tuberculous subjects, whereas a sarcoid reaction, indicating a positive result, was noted in the biopsy specimen in 28·3% of the patients with sarcoidosis. These findings differed notably from those obtained 2 years previously in a similar investigation with material obtained from the same patient, when a positive reaction was obtained in 42·4% of tuberculous patients. The authors conclude that these inconstant results are due to variability of the test material, though variations of histological interpretation are a contributory cause. They consider that in its present form the Kveim test is insufficiently reliable or reproducible to justify its use as a substitute for biopsy.

[In a letter published in a subsequent issue Nelson (*New Engl. J. Med.*, 1958, **259**, 792) criticizes the conclusions drawn by these authors.] *D. Geraint James*

Pharmacology and Therapeutics

487. **Perphenazine, a Potent and Effective Antiemetic**
S. C. WANG. *Journal of Pharmacology and Experimental Therapeutics* [*J. Pharmacol. exp. Ther.*] **123**, 306–310, Aug., 1958. 18 refs.

A comparative experimental investigation of the antiemetic effect of two phenothiazine derivatives, perphenazine and chlorpromazine, was carried out in the Department of Pharmacology, Columbia University, New York. Perphenazine was given intravenously to 80 dogs in a dosage of 0·025 to 0·1 mg. per kg. body weight 30 minutes after a meal. After a further 15 minutes apomorphine, morphine, " hydergine ", or lanatoside C was injected in emetic doses. The effect of perphenazine on vomiting induced by copper sulphate was also studied.

It was found that perphenazine was 16·6 times more effective than chlorpromazine in overcoming the effect of 0·1 mg. of apomorphine per kg. body weight, and 47·8 times more effective when the dosage of apomorphine was increased to 0·5 mg. per kg. Vomiting induced by the other test drugs was also reduced. Like chlorpromazine, perphenazine had much less effect on vomiting induced with copper sulphate. It is considered that perphenazine, like chlorpromazine, depresses the medullary vomiting centre only moderately, and that the main site of action is in the peripheral chemoceptive emetic trigger zone, where there is evidence suggesting chemical binding. Perphenazine promises to be of clinical value.
Kenneth Gurling

488. **The Effect of a Standardised Senna Preparation on the Human Bowel**
G. P. MCNICOL. *Journal of Pharmacy and Pharmacology* [*J. Pharm. (Lond.)*] **10**, 499–506, Aug., 1958. 7 refs.

A standardised senna preparation was administered to 52 ward patients in doses to each person of 1, 2, 3 and 4 tablets, and to 126 medical students in a dose of 3 tablets. Three active tablets and 3 inert tablets were also administered to each of 99 students, and one active tablet and one inert tablet to each of 44 students. With 3 tablets of senna preparation the " speed of action " with students (mean 12·15 hours) was significantly slower than that with ward patients (mean 9·7 hours). In the ward patients the frequency of griping, of looseness of stool and of multiple bowel movements increased with rising dosage. In the students' trial with one tablet there was no significant difference between the results with the active and with inert tablets; one senna tablet would appear to have a negligible pharmacological effect. Thirty-nine students and 5 ward patients experienced griping in the absence of other arbitrarily defined evidence of overdosage. The incidence of anorexia and nausea is as high with inert as with active tablets. Analysis of the results showed no significant difference in response between male and female students.—[Author's summary.]

489. **The Treatment of Cough by a Non-narcotic Antitussive**
F. GREGOIRE, Y. THIBAUDEAU, and M. COMEAU. *Canadian Medical Association Journal* [*Canad. med. Ass. J.*] **79**, 180–184, Aug. 1, 1958. 14 refs.

A controlled investigation is reported of the value of a new antitussive agent, benzononatine (" tessalon "), a derivative of butylaminobenzoic acid, which is said to have a selective anaesthetic effect on vagal fibres stimulated by pulmonary distension. An intravenous injection of 10 mg. of benzononatine controlled the " number of efforts at coughing " in 9 out of 10 healthy subjects in whom cough was induced with acetylcholine. A dose of 100 mg. of benzononatine by mouth was without effect on one further healthy subject. At the Sanatorium St-Joseph, Montreal, the drug was found to be of value in 28 patients with pulmonary tuberculosis and chronic cough, especially in a dosage of 100 mg. by mouth 4 times a day. It was helpful in patients subjected to bronchoscopy or bronchospirometry, the dose for these purposes being 5 to 10 mg. intravenously 10 minutes before the examination. There was no significant change in the results of pulmonary function tests as a result of administration of benzononatine, in spite of general clinical improvement. *I. Ansell*

490. **Gastrointestinal Intolerance to Oral Iron Preparations**
D. N. S. KERR and S. DAVIDSON. *Lancet* [*Lancet*] **2**, 489–492, Sept. 6, 1958. 22 refs.

Having observed in another investigation of iron-deficiency anaemia in pregnancy (see Abstract 572) that patients receiving a control preparation by mouth reported gastro-intestinal symptoms about as frequently as those taking iron, the authors studied the frequency of gastro-intestinal intolerance to iron in non-pregnant women, volunteers being obtained from the nursing staff of the Royal Infirmary, Edinburgh. Each volunteer was given 6 packets of pills which were to be taken, in the dosage prescribed on the packet, after meals from Monday to Friday during 6 successive weeks. A questionary concerning any symptoms experienced was completed each week, the symptoms specifically mentioned on the form being nausea, vomiting, heartburn, abdominal discomfort, constipation, and diarrhoea. The volunteers were told that the first 5 packets contained iron pills and the sixth a control pill; in actual fact the fifth box contained only lactose (the " unknown " control) pills. The iron preparations were ferrous sulphate, ferrous gluconate, ferrous succinate, and ferrous calcium citrate. The dosage of iron was standardized at 105 mg. per day.

Of 103 volunteers who started the trial, 7 failed to complete the course for various reasons unconnected with it and 3 stopped taking the pills because of unpleasant

symptoms. Of the remaining 93, only 2 complained of symptoms with the known control pills, whereas from 19 to 23 complained of symptoms when taking the iron or the " unknown " control pills. The total incidence of " side-effects " from the unknown control pills did not differ significantly from that accompanying any of the pills containing iron.

The volunteers were regrouped into those who complained of symptoms with the " unknown " control pills (20) and those who did not (73). The intolerance rate to the iron pills varied in the first group from 25% to 50% and in the second group from 16% to 22%, indicating that the first group was influenced by the commonly held belief that iron pills cause gastro-intestinal upset. There was significantly more intolerance to ferrous gluconate and sulphate in the first group, but in the second group the intolerance rates to the different iron preparations did not differ significantly. The most common symptoms were constipation and abdominal discomfort, the incidence of all other symptoms being less than 10%.

The authors conclude that a " large proportion of the symptoms experienced during iron therapy with oral preparations is psychological in origin " and true intolerance is rare. They add that it will take time to dispel the popular belief that iron pills inevitably cause unpleasant side-effects and it is worth while assuring patients that such pills should not cause gastro-intestinal symptoms. *R. F. Jennison*

491. **Clinical Studies on the Diuretic Effect of Chlorothiazide**

G. J. MAGID and P. H. FORSHAM. *Metabolism* [*Metabolism*] **7**, 589–607, Sept., 1958. 10 figs., 28 refs.

The authors of this paper from the University of California School of Medicine, San Francisco, report an investigation of the diuretic effect of chlorothiazide in a normal subject, carried out in an attempt to elucidate its mode and site of action, together with some observations on its therapeutic effect in oedematous states and in obesity. The normal subject was given single doses ranging from 250 to 4,000 mg. by mouth at 5-day intervals, urine being collected every 2 hours for determination of its electrolyte content. The rate of sodium loss increased with the dose up to 1,000 mg., after which it remained constant. Sodium excretion was greatest in the first 2 hours, when it exceeded the baseline value by about 40 mEq., and returned to normal 8 to 10 hours after a dose of 1,000 mg. Similar results were noted in respect of chloride and potassium, though in the latter case the magnitude of the loss was much smaller. Bicarbonate loss was also small and there was a 2-hour delay before its onset; on the other hand it continued to increase with doses above 1,000 mg. Sodium retention was next promoted with fludrocortisone in the same subject and the effects of chlorothiazide on electrolyte excretion compared with those of acetazolamide and meralluride. The mercurial diuretic produced a greater volume of urine with a lower concentration of sodium than the other two, though all three partially reversed the sodium-retaining effect of the steroid. The effect of chlorothiazide on the electrolyte pattern was intermediate between those of the other two, approaching more closely to that of meralluride. From these observations the authors conclude that chlorothiazide has only a minor degree of carbonic anhydrase inhibitor activity and seems to block the tubular reabsorption of both sodium and chloride. It appears to function well over a comparatively wide range of *p*H.

In the therapeutic trials a total of 48 patients were given 250 to 2,000 mg. of chlorothiazide (divided into 2 or 3 doses) daily by mouth for periods up to 6 months. All of 15 patients with congestive heart failure were improved, the best results being obtained in those with severe oedema, the diuretic efficacy of the drug appearing to fall off with reduction in extracellular fluid volume. There was little weight loss in 11 obese patients, only one of whom had overt oedema. Subjective improvement in tension, irritability, and malaise was reported by all of 5 patients with premenstrual oedema. Four patients with nephrosis showed little response; in particular, there was no change in creatinine clearance or proteinuria. An excellent diuresis was produced in 2 patients with ascites and oedema due to cirrhosis of the liver, but in one drowsiness accompanied by an alarming rise in the blood ammonia level occurred after 5 days. Chlorothiazide alone produced only a minor fall of blood pressure in 3 out of 11 cases of long-standing hypertension. However, when given in combination with the ganglion-blocking drug " inversine " (mecamylamine) it produced an additional fall averaging 48 mm. Hg systolic and 26 mm. Hg diastolic. Combination with other hypotensive drugs resulted in a smaller fall. The only side-effects noted were epigastric distress in 4 cases and a skin rash in one. The tendency to hypokalaemia was controlled by giving 1 to 3 g. of potassium chloride daily. *G. Clayton*

492. **Observations on Amanozine (W–1191–2), a Triazine Diuretic Compound**

D. V. MILLER and R. V. FORD. *American Journal of the Medical Sciences* [*Amer. J. med. Sci.*] **236**, 32–40, July, 1958. 6 figs., 1 ref.

In this paper from the Veterans Administration Hospital and Baylor University College of Medicine, Houston, Texas, a clinical trial is reported of a new oral diuretic, " amanozine ", which is a derivative of triazine. After a dose of 150 mg. twice daily water and sodium excretion were significantly increased. Doubling the dose of the drug did not lead to any further increase in the response, but caused nausea and vomiting. Water diuresis mainly occurred after the first dose and then declined in spite of the second dose. Sodium excretion was mainly raised after the second dose, as was excretion of chloride. The urinary *p*H rose. When the drug was administered over a period of 21 days there was a rise in blood urea nitrogen level and a decline in creatinine and phenolsulphonphthalein clearances.

It is concluded that this diuretic is less potent than the mercurial diuretic meralluride in respect of sodium excretion, but more potent in respect of water excretion. It appears to be relatively safe for short-term administration, but unsuitable for long-term treatment because it causes a disturbance of renal function. *R. Schneider*

493. **Carbonic Anhydrase Inhibition. IX. Augmentation of the Renal Effect of Meralluride by Acetazolamide**
T. H. MAREN. *Journal of Pharmacology and Experimental Therapeutics* [*J. Pharmacol. exp. Ther.*] **123**, 311–315, Aug., 1958. 1 fig., 10 refs.

It has been known for some time that mercurial diuretics are potentiated by metabolic acidosis and by the administration of ammonium chloride. Acetazolamide, a carbonic anhydrase inhibitor, also induces metabolic acidosis and in this paper the author reports a study of its effect in enhancing the diuretic action of meralluride in dogs. Acetazolamide was given by mouth in a dosage of 0·08 mg. per kg. body weight and meralluride in a dosage of 0·08 ml. per kg. intramuscularly. The greatest augmentation of effect occurred when acetazolamide was given at 0 and 12 hours on the first day, followed by meralluride on the second day, by which time plasma levels of acetazolamide were insignificant. The induction of metabolic acidosis on the first day led to an increase in urinary excretion of sodium, chloride, and water following the administration of meralluride on the second day as compared with the effect of the mercurial diuretic alone. The simultaneous use of both drugs was less effective, and the urinary output of base was sometimes reduced. The reason for this potentiation is thought to be renal-cell acidosis following bicarbonate loss. Hyperchloraemia did not occur and plasma chloride levels were unchanged. *Kenneth Gurling*

494. **Postoperative Analgesia with R 875. A Comparison of the Effects of *dextro*-2:2-Diphenyl-3-methyl-4-morpholinobutyrylpyrrolidine and Morphine in Man.** [In English]
V. DYRBERG and E. W. ANDERSEN. *Acta chirurgica Scandinavica* [*Acta chir. scand.*] **115**, 243–248, 1958. 13 refs.

The synthetic analgesic agent D-2:2-diphenyl-3-methyl-4-morpholinobutyrylpyrrolidine (R 875) has promising properties. In animal experiments it has been found to be 10 to 40 times more active than morphine, to be more effective when given by mouth, and to have a high therapeutic ratio. Clinically, it has proved useful in cases of severe pain. A comparison of the efficacy of R 875 with that of morphine in the control of postoperative pain is here reported from Københavns Amts Sygehus, Hellerup, Denmark.

The subjects were 144 patients aged 20 to 65 undergoing major elective surgery. The same anaesthetic technique was used in all cases and no analgesic drugs were given during anaesthesia. Either R 875 or morphine was given intramuscularly if the patient complained of pain after operation, the dose of morphine in all cases being 10 mg. and that of R 875 2·5 mg., 5 mg., or 10 mg. A second dose was given if necessary after a minimum interval of 2 hours. The patient was questioned periodically after each injection regarding the degree of pain relief (assessed on a 4-point scale) and side-effects. A double-blind procedure was used, the drugs being prepared in coded ampoules containing 1 ml. and paired in such a way that when two injections were needed R 875 was given on one occasion and morphine on the other.

The results are analysed in a number of different ways, the drugs being compared in respect of both degree and duration of pain relief. In discussing their findings the authors point out that the difficulty of obtaining an objective measure of the degree of relief of postoperative or other pain makes it necessary to adopt somewhat elaborate methods of evaluation and control. They found R 875 to be slightly more effective, weight for weight, than morphine, 7·5 mg. of R 875 corresponding in analgesic power to 10 mg. of morphine. The duration of action of the two drugs was much the same. No useful information about the side-effects of R 875 was obtained. *M. Woods*

495. **Amiphenazole and Morphine in Production of Analgesia**
S. GERSHON, D. W. BRUCE, N. ORCHARD, and F. H. SHAW. *British Medical Journal* [*Brit. med. J.*] **2**, 366–368, Aug. 9, 1958. 17 refs.

Over the past 4 years the authors have been successful in producing adequate anaesthesia without narcosis in 500 patients by administration of amiphenazole in combination with large doses of morphine. They now report from the Austin Hospital and the University of Melbourne the results obtained in 27 of these patients who were suffering from intractable pain due to advanced carcinoma. The effect of the drugs was assessed on the basis of the results of various psychological tests and the observations of the medical and nursing staff. Morphine was administered in increasing doses for a few days until narcosis or respiratory depression was produced, when amiphenazole was given in addition, by mouth or by intramuscular injection, in a dosage up to 200 mg. every 6 hours. In some cases the amiphenazole was withdrawn abruptly in order to assess the effect of such withdrawal.

From the results the authors consider that: (1) large doses of morphine (15 to 145 mg. every 6 hours) are safe if amiphenazole is also given; (2) amiphenazole prevents the drowsiness produced by morphine unless the liver is grossly damaged; (3) amiphenazole prevents addiction to morphine; (4) anaesthesia can be maintained for 24 hours; (5) the dose of amiphenazole requires to be reduced at night to allow sleep; and (6) amiphenazole should be discontinued when the patient is moribund, since narcosis is then desirable.

A possible explanation of the action of morphine and amiphenazole in combination is that they are conjugated in the liver to form a non-narcotizing analgesic substance. This would indicate that in surgical patients small doses of morphine and amiphenazole should be given for two days before operation and increasing doses immediately afterwards until adequate anaesthesia is obtained. *T. B. Begg*

496. **Agranulocytosis following Administration of Phenothiazine Derivatives**
A. V. PISCIOTTA, S. EBBE, E. J. LENNON, G. O. METZGER, and F. W. MADISON. *American Journal of Medicine* [*Amer. J. Med.*] **25**, 210–223, Aug., 1958. 6 figs., 28 refs.

Infectious Diseases

497. **ECHO Type 9 Virus Disease. Virologically Controlled Clinical and Epidemiologic Observations during 1957. Epidemic in Milwaukee with Notes on Concurrent Similar Diseases Associated with Coxsackie and Other ECHO Viruses**

A. B. SABIN, E. R. KRUMBIEGEL, and R. WIGAND. *A.M.A. Journal of Diseases of Children* [*A.M.A. J. Dis. Child.*] **96**, 197–219, Aug., 1958. 3 figs., 19 refs.

During the summer of 1957 more than 200 patients were admitted to Milwaukee Hospitals for the most part with a tentative diagnosis of nonparalytic poliomyelitis. Some of the patients had rash. Among 101 patients whose stools or cerebrospinal fluid, or both, yielded viruses in monkey kidney tissue cultures, 90 were infected with ECHO Type 9 virus, 5 with other ECHO viruses (Types 2, 14, 16, and 18), 5 with Coxsackie viruses (A9, B3, B4, and B5), and only 1 with poliovirus (Type 3). A clinical and epidemiologic survey of 2,447 families containing 11,403 persons, checked by a virologic study of 27 families with acute febrile illnesses and 25 without, led to an estimate of approximately 210 persons with ECHO 9 virus disease at home for each 1 in the hospitals. ECHO 9 virus infections were almost entirely limited to families with illness, and adults as well as children were affected. The total number of persons estimated to have been ill with ECHO 9 virus disease during the epidemic period was 40,000 for Milwaukee and environs and 28,000 for the city proper, with a population of 740,000.

Approximately 85% of ECHO 9 virus infections resulted in disease. The aseptic meningitis syndrome was often associated with only fleeting nuchal and spinal rigidity, and it is probable that many of the unhospitalized patients with pain in the neck and back may also have had involvement of the nervous system. Transitory signs of more extensive involvement of the nervous system were seen in only 6 patients; in 5 the signs suggested involvement of various regions of the medulla, and only one exhibited transitory paralysis, chiefly of the hip muscles. There were no fatalities. The rash, macular or maculopapular and only rarely petechial, was commonest in the youngest children and least common in older children and adults—77% under 5 years of age, 44% 5 to 15 years of age, and only 6% over 15 years of age. An enanthem on the buccal mucosa and tonsillar fauces was also present in some patients. Coxsackie A9 and ECHO Types 2, 14, and 16 were the only viruses recovered from a small number of patients who had febrile illnesses with rash, and it is evident that they were playing a minor role while ECHO 9 virus was playing the major role.

Antibody tests on sera obtained before and after the epidemic indicated that approximately 60% to 70% of the adult population had no previous contact with ECHO 9 virus and that only a small fraction of the total population had been infected by the time the epidemic had waned. One of the most important possible consequences of infection with ECHO 9 virus, or other similar viruses, requiring intensive study in the future, has to do with their potential role in spontaneous abortions and congenital defects.—[Authors' summary.]

498. **Abnormalities in Central Regulation of Respiration in Acute and Convalescent Poliomyelitis**

F. PLUM and A. G. SWANSON. *A.M.A. Archives of Neurology and Psychiatry* [*A.M.A. Arch. Neurol. Psychiat.*] **80**, 267–285, Sept., 1958. 9 figs., 33 refs.

From the University of Washington School of Medicine, Seattle, the authors report the clinical and physiological findings in 20 patients with central disturbances of respiratory function due to acute poliomyelitis. Three stages of involvement are described. (1) In patients in the first stage irregularity of breathing with periods of apnoea of 4 to 12 seconds was apparent only during sleep; the alveolar pCO_2 was normal during waking hours and vital capacity was never below 50%. (2) In those in the second stage the respiratory irregularity persisted into consciousness and effort by the patient was required to maintain rhythmic respiration, with the result that in many cases the patient was afraid to go to sleep. (3) Patients in the third stage showed a chaotic pattern of respiration, with varying periods of apnoea, and in these cases artificial respiration was urgently required. In both Stages 2 and 3 impaired sensitivity to CO_2 was observed, with depression of respiration on breathing 100% oxygen. Depressant drugs markedly increased this central disturbance. Post-mortem studies in 2 cases showed small areas of necrosis in the ventrolateral reticular formation of the medulla in both cases.

Although these disturbances of respiration usually cleared up spontaneously in surviving patients, disturbance of Stage 1 persisted in 2 cases for many months. Both of these patients showed CO_2 retention without dyspnoea, impairment of response to changing CO_2 tension in inspired air, and reduction of ventilation when breathing pure oxygen. One of them continued to require artificial respiration at night, but the other was able to dispense with this aid except during an attack of tracheobronchitis. In these 2 cases there appeared to be permanent abnormalities in the medullary centre. Of 9 patients with a vital capacity of less than 50% of normal who were recovering from the spinal form of poliomyelitis, 7 also had a diminished response to a stimulus with CO_2, showing that a peripheral restriction of chest movement may also affect ventilatory response to CO_2.

It is concluded that these findings support the theory that an intrinsic and sensitive function of the medullary respiratory centre is the control of rhythmicity of respiration. *E. H. Johnson*

499. **Infections Due to *Staph. aureus* in a General Hospital**
M. E. FLOREY. *British Medical Journal* [*Brit. med. J.*] 2, 403–406, Aug. 16, 1958. 15 refs.

Although only 3·8% of 11,670 patients admitted to the New York Hospital during 6 months were admitted specifically for treatment of any form of infection, the bacteriological records showed that *Staphylococcus aureus* had been isolated from no less than 5·3%. It was therefore concluded that some of these patients acquired the infection in hospital. Bacteriological investigation of every lesion suspected of being infected showed that 13·3% in surgical in-patients and 17% in medical in-patients were almost certainly infected with *Staph. aureus*. Among surgical out-patients the incidence was even higher, namely, 24 to 33%. It would thus appear that staphylococcal infection was more common than the gross figures for the hospital would suggest. Determination of the susceptibility of strains showed that although many were resistant to penicillin none was persistently so to all of 7 antibiotics tested, successful treatment thus being generally possible.

R. Hare

500. **A Contribution to the Study of the Frequency of Ocular Manifestations in Leptospirosis.** (Contribution à l'étude de la fréquence des manifestations oculaires au cours des leptospiroses)
V. VASSILEV. *Annales d'oculistique* [*Ann. Oculist. (Paris)*] **191**, 514–528, July, 1958. 45 refs.

With the aim of establishing the incidence of late ocular manifestations of leptospirosis the author, working at the Institute of Medicine, Plovdiv, Bulgaria, carried out an ophthalmological examination of 58 patients who had suffered from benign leptospirosis 9 to 12 months previously. This revealed late sequelae of iridocyclitis in 7 cases (12%). Among 93 cases of uveitis seen in the period 1955–7 serological tests for leptospirosis gave a positive result in 18 (or, after elimination of doubtful cases, 16%). During the first 6 months of 1957 10% of all cases of uveitis treated at the clinic were due to leptospirosis. The interval between the onset of the general illness and the appearance of the ocular complications varied from 24 days to 8 months. Almost all the varieties of *Leptospira* identified in Bulgaria have been known to produce disease with ocular complications.

A. A. Douglas

501. **Glandular Toxoplasmosis. A Survey of 30 Cases**
J. K. A. BEVERLEY and C. P. BEATTIE. *Lancet* [*Lancet*] **2**, 379–383, Aug. 23, 1958. 43 refs.

In this paper from the University of Sheffield the authors describe the clinical and serological findings in 30 cases of acquired " glandular toxoplasmosis "—that is, toxoplasmosis resembling infectious mononucleosis. The majority of the patients were children or young adults. The initial diagnoses included infectious mononucleosis, tonsillitis, Hodgkin's disease, lymphosarcoma, leukaemia, and aleukaemic leukaemia. The criteria for diagnosis of toxoplasmosis in this series were a dye-test titre of 1:256 and a complement-fixation titre of 1:10. In 20 cases the first symptom was swelling or pain in the lymph nodes usually of the cervical region, with, in 10 of these cases, enlargement of the axillary and inguinal nodes. In one case x-ray examination revealed enlargement of hilar lymph nodes. The spleen was enlarged in 5 cases, in 2 of which the liver was also enlarged. The consistency of the nodes varied, some being soft, some rubbery, and some hard; they remained discrete and did not break down. Resolution of the lymphadenopathy often took several months. Fatigue was common, and in some cases there was prolonged muscle pain which, it is suggested, may have been due to invasion of the muscles by the parasite. In 5 cases the enlargement of the nodes was an incidental finding. The maximum duration of symptoms was 44 weeks. There were no sequelae. Relatives of 4 of the patients had antibody titres which indicated that they had been infected at about the same time as the patients. In cats and dogs in contact with patients the dye-test titre was high; *Toxoplasma* was isolated from the brain of one cat.

The authors suggest that " toxoplasmosis accounts for 7% of cases clinically diagnosed as ' glandular fever ' but giving a negative Paul–Bunnel reaction ". Cells of the " glandular fever " type were found in the peripheral blood in 6 of the cases in this series. The possible sources of infection are discussed, but no definite conclusion is reached concerning the mode of transmission.

[This paper is important because it draws attention yet again to the commonest clinical manifestation of toxoplasmosis—generalized adenopathy. The clinical details, however, are reported at second hand.]

H. G. Farquhar

502. **Chemical Constituents of Pine Pollen and Their Possible Relationship to Sarcoidosis**
M. M. CUMMINGS and P. C. HUDGINS. *American Journal of the Medical Sciences* [*Amer. J. med. Sci.*] **236**, 311–317, Sept., 1958. 7 figs., 9 refs.

In the United States the incidence of sarcoidosis appears to be highest in the forested areas in the east of the country. The authors of this paper describe a study of a number of forest products, both chemical and biological, in which it was found that the constituents of pine pollen include an acid-fast staining lipid and an amino-acid. It was also found by infra-red spectrometry that " wax " fractions isolated from pine pollen and human-type tubercle bacilli were similar. Mycolic acid could not be demonstrated in the pine-pollen fraction by chromatographic or spectrographic techniques. The amino-acid in pine pollen was shown by paper chromatography to be similar to diaminopimelic acid. Fractionation methods also revealed that pine pollen contains phospholipid, chloroform-soluble waxes, alcohol–ether soluble lipids, and firmly bound lipids.

Suspensions of pine-pollen in paraffin oil when injected intracutaneously into guinea-pigs rendered hypersensitive to tuberculin with Freund's adjuvant evoked indurated nodules in 4 to 5 days. These nodules persisted for 10 days and then disappeared; 5 months later histological examination of the injection site revealed a tuberculoid granuloma. Pine-pollen phosphatide could also be shown to evoke an epithelioid-cell reaction.

D. Geraint James

Tuberculosis

503. **The Differential Diagnostic Significance of Gastro-intestinal Symptoms in Tuberculosis.** (Die differential-diagnostische Bedeutung gastrointestinaler Symptome bei der Tuberkulose)
E. KUNTZ. *Beiträge zur Klinik der Tuberkulose und spezifischen Tuberkulose-Forschung* [*Beitr. Klin. Tuberk.*] **119**, 24–35, 1958. Bibliography.

From the Medical Clinic of the Justus Liebig University, Giessen, Germany, the author reports a series of 300 patients with pulmonary tuberculosis, of whom 141 (47%) had mainly respiratory symptoms, 71 (24%) had both respiratory and gastro-intestinal symptoms, 25 (8%) had gastro-intestinal symptoms only, while 63 (21%) were entirely symptomless. Gastric analysis and radiological examination of the stomach were carried out in 148 cases, which were divided into three groups as follows. (1) Of 40 patients with relatively recent and predominantly exudative disease with cavitation, 25 (63%) showed hyperacidity and increased gastric motility, while gastritis was diagnosed radiologically in 6 (15%) of these cases. (2) Of 44 patients with extensive, mainly bilateral, cavitating disease, 27 (61%) had hypoacidity or anacidity with increased motility, and radiological evidence of gastritis was present in 12 (27%). (3) Lastly, of 64 patients with chronic fibro-cavernous disease, 45 (70%) showed hypoacidity or anacidity with reduced motility, and radiological evidence of gastritis was present in 28 (44%). The findings in this last group were very similar to those in alcoholic gastritis.

The author stresses the importance of gastro-intestinal symptoms in the early diagnosis of tuberculosis. In the case of the patients in this series whose symptoms were exclusively gastro-intestinal the diagnosis of pulmonary tuberculosis was delayed for at least 6 months, the patients meanwhile being referred to a wide variety of hospital departments before their true condition was discovered. *A. J. Karlish*

504. **Intermittent Combined Chemotherapy of Tuberculosis in Infants and Young Children.** (Zur Frage der kombinierten, intermittierenden Chemotherapie der Tuberkulose des Säuglings und des Kleinkindes)
H. KRUKOWSKA. *Beiträge zur Klinik der Tuberkulose und spezifischen Tuberkulose-Forschung* [*Beitr. Klin. Tuberk.*] **119**, 14–23, 1958. 3 figs., 11 refs.

From the Institute for Research in Tuberculosis, Warsaw, the author reports her experience in the treatment of 200 tuberculous infants and children, of whom 44 were aged from 3 to 12 months and 156 from 1 to 5 years. In most of these cases the disease was extensive and the state of nutrition poor: for example, one child aged 10 months weighed only 3,860 g. (9 lb.) and another aged 22 months weighed 5,860 g. (13 lb.).

Three groups of cases were distinguished as follows. (1) Disseminated tuberculosis with miliary disease of the lungs (32 cases). (2) Bronchial and paratracheal adenitis with segmental atelectasis and parenchymal infiltration (103 cases); bronchoscopic examination in this group showed that in 56 cases there was gross bronchial disease, with severe oedema, erosion of the lumen, and obstruction by large caseous masses and proliferating granulation tissue. (3) Bronchial and paratracheal adenitis, with perifocal shadowing (65 cases).

Treatment consisted in intermittent courses of relatively small doses of either streptomycin with isoniazid or isoniazid with PAS for a total period not exceeding 12 months. Individual doses of streptomycin ranged between 20 and 40 mg. per kg. body weight and the total dose rarely exceeded 10 g. The dosage of isoniazid varied from 5 to 10 mg. per kg. and that of PAS was 0·2 g. per kg. daily; in all cases the drugs were given on only 5 or sometimes 6 days in each week. The final results are stated to have been very satisfactory, but details are given of only a few selected cases. Among 32 gravely ill patients with disseminated disease there were 6 deaths, 4 of these occurring in young infants. Few toxic effects were noted and the author believes that the results of intermittent treatment are at least equal to, if not better than, those obtained by continuous administration of drugs. Larger doses are considered to be unnecessary and in many cases actually harmful.

[Further observations, including results of sensitivity tests, after a period of follow-up would be of great interest.] *A. J. Karlish*

505. **Multiple Puncture Depot Tuberculin (PPD) Cream Tests in Man**
J. PEPYS, R. A. BRUCE, and D. G. JAMES. *Tubercle* [*Tubercle (Lond.)*] **39**, 283–288, Oct., 1958. 6 refs.

The authors describe their method of testing with "depot" tuberculin, in which the tuberculin is given in an oily medium by intracutaneous injection, and compare the reactions observed with those obtained with the Mantoux test; they also investigated the reactions after B.C.G. vaccination in those subjects negative to both the Mantoux and depot tuberculin tests, and in those negative to the Mantoux but positive to the depot test. To 300 mg. of dry powdered purified protein derivative (P.P.D.) of tuberculin from the human type of *Mycobacterium tuberculosis* H37Rv was added 0·4 ml. of 0·1 N sodium hydroxide drop by drop to form a paste which was then diluted with 0·25% sodium borate to a final volume of 20 ml. containing 15 mg. of P.P.D. per ml. This paste was incorporated in various ointments, the two chiefly used being wool alcohol ointment ("eucerin anhydrous") made up as a cream containing 5 mg. of P.P.D. per g. (depot P.P.D. cream eucerin) and an ointment consisting of light liquid paraffin, 8 parts, and wool fat (lanolin), 1 part, containing 2 mg. of P.P.D. per ml. Testing was performed with Heaf's apparatus

for multiple puncture, using a depth of 1 mm. for infants and 2 mm. for older children.

In tests on 32 probationer nurses aged 18 with the first preparation concurrently with a Mantoux test the Mantoux reaction was positive in 13 (40%) and the depot P.P.D. cream test in 29 (90%). In similar tests on 489 factory workers aged 17 to 55 the Mantoux reaction was positive in 406 (83%) and the depot cream test in 451 (92%). Of 49 infants and children aged up to 14 years tested with the depot P.P.D. cream only, all gave a negative response. The second preparation was used to test 59 miscellaneous out-patients; of these, 24 (42%) were Mantoux-positive and 43 (73%) positive to the depot cream. Also giving a positive reaction to this cream were 18 out of 29 patients with sarcoidosis, all of whom were Mantoux-negative. On 32 subjects who had given a negative response to the Mantoux and cream tests B.C.G. vaccination was performed 3 weeks later and on the same day a second test with depot P.P.D. cream on the opposite arm; a reaction developed at the sites of both depot cream tests 6 weeks later, demonstrating conversion of the tuberculin reaction and persistence of the test material at the site of injection. The response to B.C.G. developed normally, but there was no reaction at the site of the Mantoux test. Lastly, performance of the B.C.G. test on 15 Mantoux-negative nurses who had been positive to the P.P.D. cream test resulted in accelerated response in 14. The reaction to the Mantoux test in 12 vaccinated nurses after a period of 4 months was positive.

The authors point out that a single depot P.P.D. cream test thus made manifest low degrees of tuberculin sensitivity, and in negatively reacting subjects local persistence of test material demonstrated tuberculin conversion after B.C.G. vaccination. It is suggested that such persistence may indeed provide a signal of naturally occurring infection in negative reactors. *V. Reade*

506. **The Use of Trypsin in the Therapy of Tuberculous Lymphadenitis and Tuberculous Fistulae**
C. RAPOPORT. *Diseases of the Chest* [*Dis. Chest*] **34**, 154–161, Aug., 1958. 2 figs., 6 refs.

At Malben's Tuberculosis Hospital, Beer Yacov, Israel, the author has treated 9 patients, 8 children aged 5 to 13 and one man, suffering from tuberculous abscesses with trypsin intramuscularly in addition to the usual chemotherapy with isoniazid, PAS, and streptomycin. The trypsin was employed in the hope that it would increase both the amount of phagocytosis by the mononuclear cells and the vascularity of the lesions, so making the tubercle bacilli more accessible to the chemotherapeutic agents. In 7 cases the abscesses had developed around tuberculous lymph nodes in the neck, mediastinum, or chest wall, while in 2 they had arisen in bone (the sternum and first right rib respectively). In every case the diagnosis was confirmed by biopsy examination, positive culture, or guinea-pig inoculation before treatment with trypsin was started. Biopsy was also performed at the end of treatment.

The case histories illustrate well how refractory tuberculous abscesses of this kind can be, showing alternately remissions and relapses in spite of prolonged chemotherapy. Also many of the fistulae had become secondarily infected. The duration of the illness extended from 4 months to 4 years, in spite of repeated chemotherapy and sometimes radiotherapy. The trypsin was given in a daily dose of 5 mg. in 1 ml. of sesame oil, 2·5 mg. being injected intramuscularly twice a day while the usual chemotherapy was continued. Within a few days fistulae started to close and there was clinical improvement, with a fall in the erythrocyte sedimentation rate. Subsequent biopsy examination showed tuberculous fibrous tissue and cultures were negative. The improvement was maintained throughout the follow-up period, which varied from 8 to 16 months. The author suggests the following regimen for these cases: 2·5 mg. of trypsin twice daily for 6 weeks, together with chemotherapy; chemotherapy continued alone for another 6 months; and finally trypsin again for 3 weeks.

[The results of this treatment appear to be promising.]
Arthur Willcox

RESPIRATORY TUBERCULOSIS

507. **Bronchoscopic Criteria for the Diagnosis of Tuberculous Lymph Node Perforation into the Bronchial Tree of the Adult. A Critical Analysis of 700 Cases**
J. ADLER, Z. HERMAN, and H. SPITZ. *Diseases of the Chest* [*Dis. Chest*] **34**, 286–298, Sept., 1958. 4 figs., 16 refs.

The authors present a retrospective analysis of the bronchoscopic findings in 700 consecutive adult patients treated for tuberculosis at Malben's Hospital, Beer Yacov, Israel, between 1951 and 1954. In no single case was unequivocal ulceration of a lymph node into the bronchus found, although in 7 the appearances were considered suggestive of such ulceration. The significance of the so-called indirect bronchoscopic signs of lymph-node perforation is hence clearly in doubt. Thus this series contained 49 cases in which " mucosal holes " were seen, an incidence which corresponds closely with the alleged incidence of lymph-node perforation reported by some workers; but the present authors show [convincingly] that in many cases such holes were the dilated and inflamed openings of the ducts of diseased bronchial nodes. In their opinion, therefore, the role of lymph-node ulceration in the perpetuation of adult phthisis remains in doubt. *P. Mestitz*

508. **Bronchial Sequelae of Primary Tuberculosis in Young Children.** (Séquelles bronchiques de primo-infection chez le jeune enfant)
P. COUVE and C. CAPPUS. *Pédiatrie* [*Pédiatrie*] **13**, 473–481, 1958. 14 refs.

The authors report the finding of bronchial sequelae in 100 cases among a large series of children aged 1 to 6 years with primary tuberculosis who were referred during a 4-year period to the Children's Sanatorium at Bullion-Longchêne, Seine-et-Oise, usually after having been treated with isoniazid and PAS for 2 to 6 months (and during the last 18 months of the period often with corticosteroids as well). They all had obvious radio-

logical lesions. The investigations consisted in bronchoscopy and bronchography. There was no decrease in the annual incidence of bronchial sequelae in succeeding years. The bronchial structural abnormalities found took the form of bronchial stenosis in 20 cases and cylindrical or saccular bronchiectasis in 80; the lesions were commoner on the right side, particularly in the middle lobe. The middle lobe was the site of the structural defect in 45 cases, the upper lobe in 38 (usually a segmental lesion), and the apical segment of the lower lobe in 17; the basal segments usually escaped. Clinically, the lesions caused little trouble. No case of post-primary tuberculosis developed during the period of observation in the segments affected, and in only 5 were there serious recurrent respiratory symptoms due to secondary bacterial infection. Operative treatment, which was undertaken in 11 cases, consisted in segmental resection in 2 cases, lobectomy in 8, and pneumonectomy in one, the operation in all cases being performed only after prolonged chemotherapy had failed to produce resolution. The immediate results have been good. The authors state that no precise indications for operative intervention can be laid down and each case must be considered on its merits, but one definite indication is the frequent occurrence of infections.

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In a pilot study carried out on 18 cases of pulmonary tuberculosis of varying type and degree of severity at Trenton General Hospital, Trenton, New Jersey, isoniazid was instilled directly into the bronchial tree on the hypothesis that it would follow the same route through the lymphatics as aspirated tubercle bacilli and so reach them in much greater concentration than can be achieved by oral treatment. (However, in all but 2 of the 18 patients so treated the usual oral treatment with isoniazid and PAS was continued, sometimes with streptomycin intramuscularly in addition.) The preparation used for bronchial instillation was 1 g. of lyophilized isoniazid in 20 ml. of sterile olive oil, and instillation (10 ml. per lobe) was carried out either by means of the standard bronchoscope or a special optical catheterizing bronchoscope (pentascope) or by the technique for bronchography. If the latter procedure was used a radio-opaque medium was made by suspending 1 g. of lyophilized isoniazid in 10 ml. of sterile olive oil and 10 ml. of " dionosil ". [The original should be consulted for details.]

Bronchial aspirates were collected before treatment and examined for tubercle bacilli by smear examination, culture, and guinea-pig inoculation, and again after treatment (when, however, they were often scanty and only sufficient for smear examination). After instillation of isoniazid there was usually increased opacity in the treated segment for about a week, with a low-grade fever but no constitutional upset. No case of oil granuloma was observed in 71 instillations. The 18 patients treated were consecutive, unselected, and ambulant. Clinical details are not given, but 2 had pleural effusions, 2 had persistent cavities, and one had bronchostenosis; the type of disease ranged from acute exudative to fibroid pulmonary tuberculosis. Of 14 of the patients whose sputum was positive before treatment, 12 converted to negative sputum in an average time of 96 days after an average of 4 instillations per patient, each instillation containing 500 mg. of isoniazid. The author considers this time for conversion to be shorter than that with conventional treatment alone. The radiological improvement was even more striking: cavities closed in all the 10 cases in which they were present and infiltration largely cleared within an average time of 55 days. There was no change in 4 cases. When improvement did occur it was maintained for an average period of 14 months. *Arthur Willcox*

510. **Results of Resection in the Treatment of Pulmonary Tuberculosis; a Statistical Study of More than 400 Cases.** (Résultats de la résection dans le traitement de la tuberculose pulmonaire; étude statistique de plus de 400 cas)
A. BONNIOT, J. BARRIÉ, and M. FINOELST. *Poumon et le cœur* [*Poumon*] **14**, 525–544, June [received Oct.], 1958.

The authors review 405 cases of pulmonary tuberculosis treated by resection at various sanatoria in the south of France since 1949. After a follow-up period of at least one year 55% of the cases subjected to pneumonectomy, 77% of those subjected to lobectomy, and 90% of those undergoing segmental resection could be classed as showing satisfactory results. As might be expected, in the cases operated on before the introduction of adequate chemotherapy in 1954 there was a high incidence of complications, broncho-pleural fistula occurring in 20% and further spread of the disease in about 23% of cases. Since that date, however, these figures have fallen to 10% and 4% respectively, and a similar improvement in results related to improved methods of treatment is reflected throughout the whole review. Thus even when a considerable amount of pulmonary disease was still present after resection satisfactory results before 1954 were obtained in only 48% of such cases, whereas in 1957 the figure rose to 77%.

Discussing their results and others reported in the literature the authors stress that these encouraging figures should not lead to undue optimism, since in the past year they have found that their postoperative complication rate has risen again. This they believe to be due to drug resistance developing in patients treated by intermittent preoperative courses of chemotherapy, and they conclude that a return to the older methods of collapse therapy will be necessary in such cases.
A. M. Macarthur

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Venereal Diseases

512. **Diagnosis of *Trichomonas vaginalis* Urethritis in the Male as a Routine Clinic Procedure**
C. S. NICOL. *British Journal of Venereal Diseases* [*Brit. J. vener. Dis.*] **34**, 192–193, Sept., 1958. 1 ref.

Over a recent 12-month period at St. Thomas's Hospital, London, a search was made for the presence of *Trichomonas vaginalis* in the genital tract in 583 male patients (466 white and 117 negro) suffering from non-specific urethritis. Urethral discharge, a urethral scrape, or centrifuged urine was examined by the moist-slide method, cultures of the discharge or scrape taken from 245 patients being prepared on Feinberg–Whittington medium. Smears and cultures were positive in 9 cases, cultures alone in 12, and smears alone in 5; in 3 others with positive smears no culture was prepared. In 484 of the remaining 554 patients the prostatic fluid was examined by the direct-slide method after treatment of the non-specific urethritis with antibiotics, *Trichomonas vaginalis* being found in 3. A diagnosis of trichomonal urethritis was thus made in 32 (5·5%) of 583 patients –14 (3%) of the white patients and 18 (15%) of the negroes. The incidence of trichomonal urethritis was higher in the older age groups compared with the incidence of gonorrhoea. Of 18 female consorts of patients suffering from trichomonal urethritis, 15 had trichomonal vaginitis. During the same period 107 male contacts of females suffering from trichomonal vaginitis were examined; 56 had non-gonococcal urethritis, including 13 with trichomonal infection.

In the author's opinion the results support the view that trichomonal infection is transmitted by sex contact, that culture is the most satisfactory diagnostic procedure, and that "the usual routine antibiotic treatment is ineffective" in trichomonal urethritis.

Leslie Watt

513. **Genital Candidiasis in Man, a Little-known Venereal Disease.** (La candidose génitale de l'homme, maladie vénérienne méconnue)
P. RIMBAUD and J. A. RIOUX. *Montpellier médicale* [*Montpellier méd.*] **53**, 757–764, May [received Sept.], 1958. 1 fig.

Describing a form of primary genital candidiasis which has been observed with increasing frequency in young adults, the authors state that *Candida albicans* is found in some 20 to 30% of healthy persons. A description is given of recent methods of isolation and identification of this fungus, which is usually considered to be "an organism of opportunity", that is, it profits by biological disturbance of the tissues, as in endocrine dysfunction or after treatment with antibiotics.

In the condition now described vulvo-vaginal infection is usually the first part of an epidemiological cycle. Thus in certain conditions, and especially after antibiotic therapy, the drug-resistant strains of *Candida* tend to flourish as the drug-sensitive micro-organisms are killed off. Also, a natural increase in the virulence of the fungus may occur, so that from being formerly mainly saprophytic it now becomes pathogenic; this change is very commonly observed in the female genital tract. The authors then describe typical clinical cases of balanoposthitis, eczema genitalis, and vulvitis, in all of which itching was a prominent symptom. Suspicion was aroused by a history of a similar condition in the sexual consort or of previous treatment with antibiotics, given either locally or parenterally. Microscopical examination and culture of the exudate confirmed the diagnosis in these cases.

The treatment advised for males is application of an ointment containing nystatin, for females the use of vaginal pessaries of nystatin combined with oral treatment with this drug. The authors stress that it is important to treat both partners simultaneously so as to avoid so-called "ping-pong" reinfection, and to observe the patients for at least a week for signs of recurrence or reinfection.

Robert Lees

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The literature on sacro-iliitis in Reiter's disease is reviewed and the close connexion between the lymphatic and venous drainage of the prostate and the sacro-iliac region is discussed. The paucity of clinical signs in sacro-iliac disease and the difficulties encountered in radiological examination of the sacro-iliac joint are emphasized. The presence, site, and distribution of backache may be helpful in diagnosis. Of a group of 73 patients with Reiter's disease at the London Hospital, radiographs of the sacro-iliac joints were obtained in all, changes being observed in 36. The changes were similar to those seen in ankylosing spondylitis and most commonly occurred in the lower portion of the joint. The earliest change was blurring of part of the joint, but later erosions and varying degrees of sclerosis developed; bony bridging was occasionally seen, and in some cases there was complete fusion of the joint. The average duration of the disease was important; in the group showing radiological abnormalities it was 12·6 years, whereas in those with normal sacro-iliac joints it was 4·8 years, suggesting that the process is chronic and the longer the duration of the disease, the more likely is it that the sacro-iliac joint will be involved. The author considers that each recurrent attack of the disease may carry with it the risk of sacro-iliac involvement. Attacks of iridocyclitis occurred in 12 of the 36 patients with sacro-iliac disease compared with 3 of the 37 with normal joints. Involvement of the sacro-iliac joints and recurrent attacks of iritis were frequently associated. It is suggested that a common but little recognized variant of

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Reiter's disease exists of which the manifestations are iritis, arthritis of the sacro-iliac joints, and genital, usually prostatic, infection. *Leslie Watt*

SYPHILIS

515. **Contributions to the Immunological Diagnosis of Neurosyphilis. II. Active Neurosyphilis with Negative Treponemal Immobilization Reaction in the Serum.** (Beiträge zur immunbiologischen Diagnostik der Neurolues. II. Aktive Neurolues mit negativem Treponemen-Immobilisations-Test (TPI-Test) in Serum)
G. FROMM and H. HIPPIUS. *Ärztliche Wochenschrift* [*Ärztl. Wschr.*] **13**, 959–961, Oct. 24, 1958. 14 refs.

It is generally agreed that the treponemal immobilization (T.P.I.) test for syphilis gives a positive result with the cerebrospinal fluid (C.S.F.) only when the result is positive also in the serum, the test being considerably less sensitive in the C.S.F. than in the serum. In cases of neurosyphilis in particular a positive T.P.I. reaction in the serum is frequently accompanied by a doubtful or negative result in the C.S.F.

Stating that so far no case has been reported in the literature in which the reaction was positive in the C.S.F. and negative in the serum, the authors, writing from the Free University of Berlin, report just such a case which occurred in a 65-year-old woman who developed clinical signs of tabes dorsalis 40 years after the primary infection. Despite 3 courses of penicillin in 3 years the condition continued to progress. The results of standard serological tests for syphilis fluctuated, being only weakly positive on occasions, but the content of cells and protein in the C.S.F. showed increasing abnormality despite treatment. Tests showed that the T.P.I. reaction was negative in the serum but positive in the C.S.F. The authors therefore conclude that this paradox may occur in rare cases, and that the finding of a negative T.P.I. reaction in the serum should not prevent an attempt being made to demonstrate immobilizing antibody in the C.S.F. in selected cases.

R. D. Catterall

516. **Method of Stabilizing Antigen Emulsion Used in VDRL Syphilis Tests**
H. N. BOSSAK and W. P. DUNCAN. *Public Health Reports* [*Publ. Hlth Rep. (Wash.)*] **73**, 836–838, Sept., 1958. 6 refs.

From the Venereal Disease Research Laboratory, U.S. Public Health Service, Chamblee, Georgia, a method is described of preparing a stable antigen emulsion of standard reactivity for use in the V.D.R.L. slide, tube, and cerebrospinal-fluid tests for syphilis. A stock 1% alcoholic solution of benzoic acid is prepared by dissolving 1 g. of benzoic acid (reagent grade) in 100 ml. of absolute ethyl alcohol and stored in a glass-stoppered flask at 6 to 10° C. V.D.R.L. antigen emulsion is prepared in 10-ml. volumes as described in the standard method. To each 10-ml. volume of freshly prepared material 0·1 ml. of the 1% solution of benzoic acid is then added so that the final concentration is 0·01%.

Each aliquot of this stabilized emulsion is tested with control sera and all those of standard reactivity are pooled. The pool is dispensed in convenient volumes of 5 or 10 ml. in screw-capped vials. The stabilized emulsion was shown to be satisfactory for use on 7 consecutive days after storage at 6° to 10° C. for periods of 4 to 6 weeks: in one instance an unopened vial was refrigerated for 4 months and found to be of standard reactivity when tested. A comparison of the results of 570 tests with the freshly prepared and with the stabilized emulsion by the slide-test technique indicated that benzoic acid does not affect reactivity levels and was the most satisfactory of a number of substances tested.

R. R. Willcox

517. **Fractionation of TPI Antibodies and Wassermann Reagins.** [In English]
A. B. LAURELL and B. HEDERSTEDT. *Acta pathologica et microbiologica Scandinavica* [*Acta path. microbiol. scand.*] **44**, 88–91, 1958. 1 fig., 6 refs.

Paper electrophoresis was carried out at the State Bacteriological Laboratory, Stockholm, on sera from 5 patients with secondary or late syphilis by the method described by Laurell (*Acta path. microbiol. scand.*, 1955, Suppl. 103), the strips being cut transversely into pieces from which the protein fractions were then recovered by centrifugation. The treponemal immobilization (T.P.I.) test and the Wassermann reaction (using cardiolipin and cholesterolized human heart as antigens) were performed quantitatively on the fractions thus isolated.

Treponemal immobilizing antibody was found to migrate with the γ-globulin fraction, while the Wassermann reagins were located in the γ- and β_2-globulin fractions, some sera showing two distinct reagin peaks. The T.P.I. antibody is therefore distinct from the reagin migrating with the β_2 globulins. Its relationship to the Wassermann antibody found in the γ-globulin fraction, however, remains uncertain, as the method of separation did not yield sufficient material for absorption tests to be carried out. *A. E. Wilkinson*

518. **Reiter's Protein Complement-fixation Test. Report of a Trial in 1,000 Unselected Cases**
W. D. FOSTER, C. S. NICOL, and A. H. STONE. *British Journal of Venereal Diseases* [*Brit. J. vener. Dis.*] **34**, 196–197, Sept., 1958. 4 refs.

The authors carried out the Reiter protein complement-fixation test (R.P.C.F.T.) in parallel with the Wassermann reaction (W.R.) with cardiolipin antigen and Price's precipitation reaction on 1,000 unselected patients attending the Venereal Disease Department at St. Thomas's Hospital, London. The technique of the R.P.C.F.T. was modelled as closely as possible on that of the W.R., the only modification found necessary being that the antigen, serum, and complement were left in contact overnight in the refrigerator and brought up to 37° C. before addition of the haemolytic system. [For practical details the original paper should be consulted.]

One or more of the tests gave positive results in 288 cases, which fell into three groups: (1) 178 cases of clinically positive syphilis in which the R.P.C.F.T. and

one or other or both of the other tests gave positive results; (2) 13 cases in which the R.P.C.F.T. gave a negative result although one or other or both of the other reactions was positive—8 of these were cases of treated syphilis and the remaining 5 had no clinical evidence of treponemal infection; (3) 97 cases in which the R.P.C.F.T. gave a positive result and both the other tests gave negative results. The treponemal W.R. gave positive results in 51 out of 79 cases in Group 3. Of the 97 patients in this group (77 of whom were coloured), all but 15 gave a history of syphilis or yaws.

From this evidence it is concluded that the R.P.C.F.T. is more sensitive and specific than the standard W.R. and, being no more difficult to perform, is suitable for routine use. *F. Hillman*

519. **The Problem of the Biological False Positive Reaction in Serological Tests for Syphilis.** (Zur Frage des biologisch falsch positiven Reaktionsausfalles serologischer Nachweisverfahren der Syphilis)
W. HARTL. *Zeitschrift für klinische Medizin* [*Z. klin. Med.*] **155**, 379–402, 1958. 3 figs., 43 refs.

This paper from the University Medical Clinic, Marburg, reports the finding of a biological false positive reaction to standard serological tests for syphilis (S.T.S.) in 150 sera out of a total of 4,679 specimens examined, an incidence of 3·2%. In the majority of cases the phenomenon was acute. The author considers that the commonest precipitating factors responsible for the acute reaction are bronchopneumonia of varying aetiology, active pulmonary tuberculosis, glandular fever, subacute bacterial endocarditis, infective hepatitis, hepatic cirrhosis, rheumatoid arthritis, and certain forms of thrombophlebitis. A battery of serological tests was used in all cases, but the treponemal immobilization test in only a few. Of 3 patients who were classified as chronic false positive reactors—the phenomenon being present for a period of at least 6 months—one had disseminated lupus erythematosus, one chronic hepatitis, and the third thrombophlebitis in the legs. The results of the various serological tests employed are described in detail [but clinical information about the patients is scanty].

The author [rightly] points out the importance and difficulty of distinguishing between cases of latent syphilis and those giving a false positive reaction. He also stresses the grave consequences, particularly in pregnant women, of diagnosing syphilis in a patient in whom such an infection has never occurred.

R. D. Catterall

520. **Studies on the Effect of Variation of Concentration and Origin of Lecithin (Natural and Synthetic) in Cardiolipin Complement-fixation Antigen**
A. REYN and M. W. BENTZON. *British Journal of Venereal Diseases* [*Brit. J. vener. Dis.*] **34**, 169–176, Sept., 1958. 4 figs., 28 refs.

After a review of the relevant literature the authors describe investigations carried out at the State Serum Institute, Copenhagen, to study the effect on sensitivity of using various natural and synthetic lecithins in various concentrations (the concentrations of the cardiolipin and cholesterol components being kept constant) in the preparation of the cardiolipin complement-fixation antigen for the serological diagnosis of syphilis. International Reference Preparations of egg (E) and beef-heart (B) lecithin and the synthetic L-α-dioleyl (DO) (unsaturated) and L-α-dimyristoyl (DM) (saturated) lecithins were used, with an International Reference Preparation of cardiolipin and cholesterol precipitated from ethanol. Complement-fixation antigens containing the various lecithins in concentrations ranging from 1/16 to double the "normal" value (0·0875% w/v) were prepared and stored at room temperature and at 56° C. for various periods up to 5 months before testing against human freeze-dried positive syphilitic and biologically false positive sera of the acute and chronic types by the quantitative method of Mørch.

Increasing the concentration of DM lecithin in the antigen decreased its sensitivity. Thus the antigen with a "normal" concentration of DM lecithin was slightly less sensitive than the reference antigen with E lecithin in "normal" concentration and that with double the "normal" concentration of DM lecithin even less so. Antigens containing different concentrations of DO lecithin varied in sensitivity in the same way, but were slightly more sensitive than the antigens containing the same concentrations of the saturated lecithin. In order to obtain antigens of "standard sensitivity" it would be necessary to use DM lecithin in about half the "normal" concentration and DO lecithin in about 1·5 times the "normal" concentration. However, the sensitivity of the antigens is probably influenced by the number of double bonds in the fatty acids of the lecithins used and there is always the risk that occasional sera will respond differently to antigens made up with lecithins from different sources. The specificity of antigens prepared with DM and DO lecithins was not tested, but DO lecithin gave a stronger reaction with biologically false positive sera than DM lecithin.

Antigens made up with double the "normal" concentration of the natural lecithins were also less sensitive than those with the "normal" concentration, while those with half the "normal" concentration were more sensitive, though the difference was significant only for E lecithin and with one particular batch of sera. The effect of varying the concentration was more marked with E than with B lecithins. Storage of the antigen made up with half the "normal" concentration of E lecithin at 56° C. for about 5 months resulted in a loss of sensitivity against all syphilitic sera and a variable loss against biologically false positive sera. Antigen with a "normal" concentration of E lecithin similarly stored showed no loss of sensitivity against acute sera, but a greater loss against chronic sera. Antigens containing the "normal" concentration of B lecithin showed a slight gain in sensitivity on storage.

It is suggested that in comparing new with old reference batches antigens containing cardiolipin, lecithin, and cholesterol in the "normal" concentrations and also "in the neighbourhood" of these concentrations should be prepared as a guarantee against the risk of gradual systematic changes in the potency of the reference preparations. *F. Hillman*

Tropical Medicine

521. **Anaemia of Uncertain Origin in Infancy**
R. G. HENDRICKSE and M. A. R. KING. *British Medical Journal* [*Brit. med. J.*] **2**, 662–669, Sept. 13, 1958. 5 figs., 20 refs.

Severe anaemia during the first 2 years of life which is not due to the sickle-cell gene or to other recognizable diseases is often seen in patients admitted to University College Hospital, Ibadan, Nigeria, and in this paper are reported the results of investigation and treatment of 24 such patients, whose average age was 9½ months. The presenting clinical features were fever, cough, vomiting, and hepato-splenomegaly. All except one of the patients were breast-fed. The anaemia was normochromic or slightly hypochromic, and anisocytosis, poikilocytosis, and polychromasia were common. The reticulocyte count averaged 5% of the total erythrocytes and the marrow showed a normoblastic hyperplasia. In 2 cases the plasma volume fell with treatment. The plasma protein levels did not differ from those observed in non-anaemic infants. The values obtained with both the thymol turbidity and the zinc sulphate turbidity tests, however, were abnormally high, although the serum bilirubin level in all except 3 infants was normal. Malarial infection due to *Plasmodium falciparum* was present in 13 cases. No evidence of iron deficiency or of malnutrition was found. There were 2 deaths in the series; in the remaining patients the anaemia improved rapidly following treatment with chloroquine, supplemented when necessary with blood transfusion.

It is considered that malaria is the main cause of the anaemia. The absence of evidence of gross haemolysis or haemorrhage in anaemic patients with active erythropoiesis is stressed, and it is suggested that hypersplenism and changes in plasma volume may be pathogenetic factors.

J. L. Markson

NUTRITIONAL DISORDERS

522. **Deficient Salt Intake in Weaned Infants and Climatic Factors in Malnutrition of the Kwashiorkor Type in Rabat.** (Carence alimentaire en sel après sevrage et facteurs climatiques au cours des malnutritions type kwashiorkor à Rabat)
C. PAQUE. *Presse médicale* [*Presse méd.*] **66**, 1572–1575, Oct. 11, 1958. 3 figs., bibliography.

Deficiency disease of the kwashiorkor type has been found to have a seasonal incidence in the subtropical region of Rabat on the Moroccan coast, the majority of cases occurring towards the end of the hot, dry season. Similar observations have been reported from other parts of North Africa and from Central America. A study of 92 cases of this type of malnutrition admitted to the Hôpital Avicenne, Rabat, during the 3 years 1955–7 showed that newly weaned infants suffered most intensely, while the symptom complex of polydipsia, polyuria, anorexia with loss of weight, intense lethargy, and the aggressiveness of "water sickness" indicated a serious salt deficiency which, in the author's opinion, is due to climatic factors.

When the Moroccan infant is weaned it exchanges a diet of milk, with a high sodium chloride content, for one of sweet, farinaceous foods with little or no salt content. Large-scale dietary studies have shown that there is no significant seasonal variation in the diet of children aged 1 to 3 years. However, bioclimatological studies along the lines developed by Thornthwaite, whereby the climate is defined in terms of its effect on the fluid balance of the living organism, show that in this region there is a steep rise in the "aridity index" between June and October. This causes profuse sweating and a consequent heavy loss of water, which is readily replaced, and of salt, which the child is unable to replace from dietary sources. As a result towards the end of the hot season its serum chlorides are seriously depleted, water cannot be retained in the body, and despite increasing polydipsia a condition of extracellular dehydration develops. At the same time a state of protein deficiency results from the excessive dilution of the intracellular contents consequent on the osmotic imbalance.

All the cases studied by the author showed oedema, hypoproteinaemia (less than 5 g. per 100 ml.), and loss of pigmentation, with no albuminuria. Three stages in the development of the syndrome are noted: (1) Dehydration due to salt deficiency with minimal protein deficiency and no oedema; this stage is seldom seen in hospital. (2) Severe dehydration due to salt deficiency combined with marked hypoproteinaemia leading to gross oedema of the extremities; without treatment this progresses until the full kwashiorkor syndrome is present. (3) Anasarca with anuria and intracellular hyperhydration. It is suggested that chronic salt deficiency may account for the inability of the organism to utilize protein which has been noted in kwashiorkor.

The author considers that bioclimatological factors should be taken into consideration in the study of all forms of nutritional deficiency peculiar to tropical and subtropical regions. His findings in Morocco suggest that similar studies might prove of value in countries with comparable bioclimatic conditions, such as Pakistan and part of Australia, and in Northern Nigeria, where kwashiorkor has a similar seasonal incidence.

M. R. Medhurst

523. **Malnutrition in Uganda. Examination of an Official Statement**
J. MCFIE. *Lancet* [*Lancet*] **1**, 91–94, Jan. 10, 1959. 27 refs.

INFECTIOUS DISEASES

524. **Pneumonia among Africans in Uganda**
H. M. LEATHER. *Thorax* [*Thorax*] **13**, 222–228, Sept., 1958. 2 figs., 8 refs.

Pneumonia is common among East Africans and a frequent cause of death. The aetiology and clinical course of the disease were studied in 52 African patients (44 male and 8 female) with pneumonia admitted to Mulago Hospital, Kampala, Uganda, between September, 1955, and May, 1956. In 37 of the 52 cases bacterial pneumonia was diagnosed (pneumococcal in 34 and staphylococcal in 3), organisms being isolated from specimens of sputum or from laryngeal swabs. No organisms were cultured in the remaining 15 cases, but in 9 the cause was considered to be bacterial, while in 6 the findings were suggestive of aspiration pneumonia. Specimens of serum from the last 17 cases in the series were examined at the Central Public Health Laboratory, Colindale, for immune bodies to influenza viruses A, B, and C, the adenoviruses, the rickettsiae of Q fever, the psittacosis–lymphogranuloma-venereum group of viruses, and for *Streptococcus* M.G. agglutination. In one of the 17 cases there was evidence of recent influenza-A infection.

Anatomically, the cases fell into 4 groups—lobar pneumonia (12 cases), lobar pneumonia with segmental affection of other lobes (10 cases), segmental pneumonia (26 cases), and lobular pneumonia (4 cases). In pneumococcal pneumonia the commonest distribution was segmental or polysegmental. Of the 3 deaths in the series, 2 occurred in patients with staphylococcal pneumonia; in the remaining cases there was usually a rapid response to chemotherapy. *R. R. Willcox*

525. **A Modification of the Lepromin Test**
J. A. K. BROWN. *Leprosy Review* [*Leprosy Rev.*] **29**, 184–196, Oct., 1958. 7 figs., 5 refs.

The author describes an investigation, carried out during the past 4 years in Uganda, of various practical modifications of the lepromin test. As the supply of this antigen is naturally limited, attempts have been made to use it in diluted form, but without much success. In a preliminary investigation the author confirmed that dilution of the antigen depressed the reaction; thus with a dilution of 1:20 positive reactions were obtained in only 86% of 269 known lepers, while this proportion fell to 37% with a dilution of 1:750.

The author then investigated the possibility of using the Heaf multipuncture apparatus (as used for tuberculin testing) for injecting the antigen; this instrument produces 6 small intradermal punctures arranged in a ring, and a reading was considered positive when a discrete induration became palpable at 4 of these 6 points. The lepromin was used in two strengths, 1:20 and 1:100, with the addition of 10% glycerin. The reactions to the two dilutions could be correlated with each other by adding 25% to the measurement of the reaction to the weaker antigen. A series of 192 patients with leprosy, none of whom was clinically lepromatous, were tested by the multipuncture method and 27 of them simultaneously by the usual intradermal inoculation. All these 27 had tuberculoid leprosy and gave a positive Mitsuda response to the intradermal injection, but only 12 of them responded with a ring of papules to the multipuncture test. The number of positive multipuncture reactions reached a peak (149 out of 192 patients investigated) at the end of the second week. A further group of 23 patients who had been Mitsuda-positive a year earlier and showed a positive reaction to the multipuncture test were reinvestigated simultaneously by both methods; with the Mitsuda technique the reactions were now all stronger, whereas with the multipuncture technique none was stronger. The author concludes that when the two reactions are performed simultaneously the reaction to the larger dose suppresses that to the smaller.

In a further study on 368 cases of leprosy the multipuncture lepromin test was performed on one forearm and the tuberculin test with P.P.D. on the other. In 228 out of 336 available cases (66%) the results of the tests, whether positive or negative, coincided. In the remaining one-third equal numbers were positive to one test and negative to the other and vice versa. A "depot" preparation of lepromin, produced by grinding lepromatous tissue in a mixture of liquid paraffin, lanolin, and saline, was comparable in effect with the usual reagent. It is concluded that the multipuncture test could be usefully employed in field surveys together with the tuberculin test. It is economical of antigen (an important consideration), is easy to apply, and can be quickly read.
William Hughes

526. **Antimalarial Drugs in Nigeria: Results of a New Survey**
L. J. BRUCE-CHWATT and D. W. HORN. *British Medical Journal* [*Brit. med. J.*] **2**, 869–876, Oct. 11, 1958. 26 refs.

The chemotherapy of malaria has made considerable progress since the senior author's first survey, reported some 8 years ago (*Brit. med. J.*, 1950, **2**, 7; *Abstr. Wld Med.*, 1950, **8**, 557). For the purpose of the present survey a medical questionary on the prophylaxis and treatment of malaria was sent to 380 doctors practising in Nigeria and a non-medical questionary to a group of Lagos residents (mainly non-immune expatriates of non-African origin). The medical questionary enquired as to the age, sex, and number of patients with malaria seen during the year, the type of prophylactic drug prescribed and regularity of administration, the practitioner's favoured type of treatment, any toxic effects observed, and the views of the practitioner on malaria prophylaxis and treatment of Africans and expatriates. The non-medical questionary asked for information on the respondent's nationality, age, sex, and duration of stay in Nigeria and in Lagos, the type of antimalarial drug taken and its dosage, on whose advice and how regularly, reason for change of drug (if any), the number of attacks of malaria, and by whom diagnosed.

Of 380 doctors questioned, 146 (38·5%) gave complete replies and of these 128 practised outside Lagos and had 6,859 expatriates under their care; the replies from the Lagos residents produced information on 2,222 persons. The results, which were transferred to punched cards and analysed statistically, showed that the incidence of malaria in expatriates in Nigeria fell from 225 per 1,000

in 1949 to 142 per 1,000 in 1956, while in the total expatriate population of nearly 18,000 there were only 2 deaths, one due to malaria and one to blackwater fever after an injection of quinine. In the town of Lagos the incidence fell from 149 per 1,000 in 1948 to 60 per 1,000 in 1956. A comparable group of British Army personnel and their families (about 1,000 persons) showed a malaria rate of only 25 per 1,000 in 1956, a difference in incidence which tends to confirm the impression that some cases of malaria among civilians are due to lapses in regular prophylaxis.

Chloroquine was the most popular drug for the treatment of malaria, with mepacrine second and amodiaquine third. Quinine by injection (mostly intramuscular) was still being used for severe malaria. For prophylaxis proguanil was the most favoured drug, followed by pyrimethamine and chloroquine. So-called "breakthroughs" occurred in about 6% of persons whichever drug was used, suggesting that many of the failures were due to an inadequate prophylactic regimen or to undiagnosed non-malarious fevers. Of the people who changed drugs, the greatest number changed from proguanil to pyrimethamine and most of these were children. Mepacrine and quinine are now little used as prophylactics by expatriates resident in Nigeria. Gastro-intestinal upset was the commonest side-effect attributed to any drug. The intramuscular injection of 100 to 150 mg. of mepacrine musonate caused an epileptiform seizure in 37 children under the age of 3, which was fatal in 29 cases. Psychosis due to mepacrine taken by mouth was reported by 36 doctors, while chloroquine injections produced epileptiform fits in 2 infants. Apart from gastro-intestinal upset, the most common side-effects of oral administration were pruritus and blurring of vision. Pyrimethamine caused no side-effects in standard dosage, but there were 7 cases of acute accidental poisoning in young children who had gained access to tablets of this drug. Prompt medical action saved the lives of 2 of these too adventurous experimenters. The estimated cost to the Government of Nigeria of all antimalarial drugs used in 1956, both prophylactically and therapeutically, was about £60,000.

[This paper contains a wealth of information which has not previously been available. It should be read in detail by all concerned with the prophylaxis and treatment of malaria.] *L. G. Goodwin*

527. **Malaria and Prematurity in the Western Region of Nigeria**

D. S. H. CANNON. *British Medical Journal* [*Brit. med. J.*] **2**, 877–878, Oct. 11, 1958. 7 refs.

Out of 392 newborn African babies 30% had a placenta infected with malaria parasites. The mean birth weight in the 130 newborn that had an infected placenta was 11 oz. (312 g.) less than the birth weight of 262 whose placenta was not infected. There were 37% of premature babies in deliveries where the placenta was found infected with malaria parasites; in deliveries with non-infected placenta the respective figure was 12%. There was no case of congenital malaria among 117 newborn, 25·6% of whom had an infected placenta. There appears to be a negative correlation between frequency of infection of the placenta and the parity of the African mother.—[Author's summary.]

[The percentage of babies weighing less than 5½ lb. (2,500 g.) was higher in the malarious group at each parity.—EDITOR.]

528. **Steroids as a Supplementary Treatment in Late Leishmaniasis. A Preliminary Report**

A. DOSTROVSKY. *British Journal of Dermatology* [*Brit. J. Derm.*] **70**, 288–292, Aug.–Sept., 1958. 15 refs.

In cases of leishmaniasis (local dermal type) subcutaneous injection of leishmanial antigen (the leishmanin test) produces within 48 hours a local inflammatory reaction similar to the tuberculin reaction, which persists for many weeks. The reaction can be prevented completely by local injection of hydrocortisone (but not other steroids) or it can be reduced by giving cortisone internally over a long period. These findings indicate that steroids have some value in preventing the development of chronic granulation tissue in leishmaniasis.

At Hadassah University Hospital, Jerusalem, 8 patients with late leishmaniasis which had failed to respond to other forms of treatment were given a number of courses, each lasting several months, of 30 injections of stibophen (3 to 5 ml. twice weekly) with 150 to 300 mg. of cortisone by mouth daily. Since this dosage of cortisone seemed insufficient completely to reduce the local lesions, 0·1 to 0·2 ml. of a suspension of hydrocortisone (equivalent to 2·5 to 5 mg.) was injected intradermally over the lesions twice a week. The author states that these injections are painful and that "exact deposition" in the skin is difficult; they may also cause local irritation and yellow streaks may occur at the site of injection. Good therapeutic results were, however, usually obtained. In patients who did not tolerate stibophen, streptomycin with steroids sometimes produced a good response.

It is considered that steroid therapy may be helpful in late cases of leishmaniasis which have resisted other treatment. *F. Hawking*

529. **Post-schistosomal Uropathy**

D. M. FORSYTH. *Lancet* [*Lancet*] **2**, 990–992, Nov. 8, 1958. 5 refs.

The syndrome of post-schistosomal uropathy is briefly discussed and 6 cases treated at the hospital of the Kuwait Oil Company, Ahmadi, are described. All the patients were cured of urinary schistosomiasis following injection of organic antimonials; 2 patients were also given lucanthone. Although the helminthic infection was eradicated, dysuria, urgency, frequency, and haematuria recurred as a result of pyogenic infection of the damaged urinary tract. Hydronephrosis or hydroureter was present in 3 cases, and one patient had calculi in the ureter. The author considers that post-schistosomal uropathy is common and that the prognosis is poor unless corrective surgical measures are possible. The signs and symptoms resemble those of a recurrence of schistosomiasis, but further specific treatment may be dangerous and is unnecessary unless viable ova are found in the urine. *L. G. Goodwin*

Nutrition and Metabolism

530. **Factors Affecting the Absorption of Vitamin B_{12}**
B. F. CHOW, J. M. HSU, K. OKUDA, R. GRASBECK, and A. HORONICK. *American Journal of Clinical Nutrition* [*Amer. J. clin. Nutr.*] **6**, 386–393, July–Aug., 1958.

Data have been presented to show that absorption of vitamin B_{12} [cyanocobalamin] can take place in subjects without a stomach. Therefore, it must occur in the intestines or sublingually. Absorption can be increased by the divided dosage schedule. The absorption of vitamin B_{12} in clinically healthy subjects is partially dependent on the physical state in which it is administered. Vitamin B_{12} given in aqueous solutions to normal subjects is better absorbed than that given in a specific type of capsule. Vitamin B_{12} absorption is also impaired by vitamin B_6 deficiency, and can be improved by subsequent administration of pyridoxine.—[Authors' summary.]

531. **The History of Pellagra, Its Recognition as a Disorder of Nutrition and Its Conquest**
V. P. SYDENSTRICKER. *American Journal of Clinical Nutrition* [*Amer. J. clin. Nutr.*] **6**, 409–414, July–Aug., 1958.

532. **Tobacco Amblyopia: a Clinical Manifestation of Vitamin-B_{12} Deficiency**
J. M. HEATON, A. J. A. MCCORMICK, and A. G. FREEMAN. *Lancet* [*Lancet*] **2**, 286–290, Aug. 9, 1958. 44 refs.

The possibility that tobacco amblyopia may be one of the clinical manifestations of vitamin-B_{12} (cyanocobalamin) deficiency was investigated in 14 cases at the Bristol Eye Hospital, the investigation being prompted by a statement by Duke-Elder (*Textbook of Ophthalmology*, London, 1954) that large doses of the vitamin are effective in relieving this condition.

Only in 3 of the 14 cases was the haemoglobin level less than 90%; 2 of these patients had histamine-fast achlorhydria and a megaloblastic bone marrow. Neurological features suggestive of vitamin-B_{12} deficiency were present in 5 cases and a sore, red, smooth tongue in 4. The serum vitamin-B_{12} level was estimated by microbiological assay with *Euglena* in 13 cases and ranged from 15 to 350 $\mu\mu$g. per ml., the mean being 218 $\mu\mu$g. per ml., whereas in 12 control subjects the range was 280 to 1,000 $\mu\mu$g. per ml. and the mean 538 $\mu\mu$g. per ml. Vitamin B_{12} was given parenterally in doses of 100 μg. twice weekly for a month and then less frequently for at least 6 months to 9 patients, 3 of whom continued smoking as heavily as before. All these patients recovered more rapidly than would have been expected with orthodox treatment (prohibition of smoking and vitamin-B complex by mouth). The findings are discussed at length in relation to the effects of vitamin-B_{12} deficiency, and it is concluded that in persons with even a mild deficiency of the vitamin the retina or optic nerve is unduly sensitive to tobacco. *G. S. Crockett*

533. **Excretion of Fluid in Malabsorption States**
R. MISK, B. A. SCOBIE, and W. H. J. SUMMERSKILL. *Lancet* [*Lancet*] **2**, 390–392, Aug. 23, 1958. 4 figs., 15 refs.

At the Central Middlesex Hospital, London, the authors studied water excretion in 14 patients suffering from various forms of the malabsorption syndrome, including idiopathic steatorrhoea, regional ileitis, tuberculous enteritis, and jejunal diverticulosis. The patients received tap-water (20 ml. per kg. body weight) by mouth or 5% dextrose solution (15 ml. per kg. body weight) intravenously. Diuresis was impaired in all as compared with that in 19 controls. A correlation was observed between the severity of the disease and the impairment of water excretion, but there was no relationship between the latter and intestinal distension, lowering of the serum potassium and serum albumin levels, or the presence or absence of histological changes in the mucosa. The authors point out that although impaired intestinal absorption of water is a feature of idiopathic steatorrhoea, this cannot account for impairment of diuresis after intravenous administration of water. In no case was there evidence of overt kidney disease. It is concluded that the impaired water excretion is due to a "profound metabolic disorder . . . possibly implicating adrenocortical or neurohypophyseal function". *R. Schneider*

534. **Marked and Sustained Blood Cholesterol Lowering Effect by Medication with Niacin and Pyridoxine**
M. G. GOLDNER and L. E. VALLAN. *American Journal of the Medical Sciences* [*Amer. J. med. Sci.*] **236**, 341–352, Sept., 1958. 2 figs., 9 refs.

The effect of nicotinic acid (niacin) on hypercholesterolaemia was studied at the Jewish Chronic Disease Hospital, Brooklyn, New York, in 53 patients (45 of them in-patients) with clinical evidence of advanced degenerative vascular disease, in all but 5 of whom the serum cholesterol level was above 250 mg. per 100 ml. The patients ranged in age from 30 to 96 years and included 10 with diabetes, 3 with myxoedema, and one with familial hypercholesterolaemia. All the in-patients were kept on a low-fat diet (50 g. fat, 100 g. protein, 250 g. carbohydrate) supplying about 2,000 Cal. The nicotinic acid was combined in a tablet with pyridoxine (which, it was thought, might potentiate its effect), other vitamins, reserpine, and pentylenetetrazol (leptazol).

To one group of 20 patients nicotinic acid was given continuously for 10 weeks in a daily dose of 2 or 3 g. By the end of this period the mean blood cholesterol level had fallen by 39%—from 338 to 203 mg. per 100 ml. Some reduction in the cholesterol level was observed in every case within 2 weeks of starting medication. When the drug was withheld the serum cholesterol level rose markedly within 2 to 3 days, but fell again as early as

48 hours after the resumption of treatment. In view of the observation of Altschul *et al.* (*Arch. Biochem.*, 1955, **54**, 558) that some hypocholesterolaemic effect was produced by a daily dose of only 1 g. of nicotinic acid, the effect of still lower doses was studied in other groups of patients. While 100 mg. a day was ineffective, 200 mg. a day had a small but sustained effect on the serum cholesterol level, an average reduction of about 13% being obtained after 4 to 8 weeks' treatment in the 6 " representative " cases for which data are given.

The most disturbing side-effect was flushing and lightheadedness. All patients who, at the beginning of the experiment, were given nicotinic acid alone experienced this, and although the addition of the other drugs brought about some improvement, 15 patients refused the compound tablet after one week. Nausea and occasional vomiting occurred, but could be prevented by giving the tablets together with meals. A few patients complained of palpitation and others of voluminous fatty stools, sometimes with diarrhoea. All patients showed an increase in appetite and in activity. The fasting blood sugar level was not affected, and serial tests showed no significant change in liver function.

[The reduction of the serum cholesterol level reported is greater than that obtainable by any other method, and it would be interesting to know how long treatment with nicotinic acid can be successfully maintained. The low incidence of serious side-effects observed in these short-term experiments may perhaps be attributable to the other drugs given, which amounted to 4·5 mg. of pyridoxine, 9 mg. of thiamine, 18 mg. of riboflavin, 180 mg. of ascorbic acid, 9 μg. of cyanocobalamin, 180 mg. of leptazol, and 0·225 mg. of reserpine when the daily dose of nicotinic acid was 3 g.] *Z. A. Leitner*

535. **The Role of the Nervous System in the Pathogenesis of Certain Forms of Obesity and Their Response to Dietetic Treatment.** (Роль нервной системы в патогенезе различных форм ожирения и изменение ее под влиянием лечебного питания)
A. M. Stepanjan-Tarakanova, L. Ja. Golubeva, and V. K. Zikeeva. *Проблемы Эндокринологии и Гормонотерапии* [*Probl. Endokr. Gormonoter.*] **4**, 52–64, July–Aug., 1958. 7 figs., 30 refs.

In the authors' opinion obesity is due in a large number of cases to neuro-endocrine factors which are difficult to assign to any specific region of the central nervous system, electroencephalographic (EEG) changes showing evidence in some cases of lesions of the cerebral hemispheres, in others of damage to some part of the hypothalamus. Such lesions may be due to encephalitis following diseases such as measles or pertussis or to brain trauma. In the hypothalamic group (to which most of the younger patients belong) obesity is usually accompanied by other hypothalamic symptoms such as somnolence, inverted sleep-rhythm, diabetes insipidus, and disturbance of temperature regulation or by endocrine symptoms such as hyperadrenocorticism, hypogonadism, or hypothyroidism. In adults the highest incidence is in the fourth decade among women and about 10 years later in men.

The 130 patients reported in this study were grouped in three categories: (1) cerebral or neuro-endocrine (79 cases); (2) endocrine (26); and (3) metabolic alimentary (25). In Group 1 the EEG findings were diagnostic of primary organic damage to the central nervous system. In Group 2 certain secondary or functional disturbances in the cerebral hemispheres were indicated. In Group 3 no sign of organic damage to the central nervous system was found, though some functional disorder was often present (for example, increased tendon reflexes, punctate hyperalgesia, or emotional lability). The most frequent EEG abnormalities were the presence of delta waves in basal and anterior cerebral leads (frontal and precentral) and irregular diffuse alpha rhythm of low amplitude, indicative of an inhibitory process. It is suggested that the regulating role of the central nervous system is shifted in an inhibitory direction in (1) cases of severe primary organic damage to the nervous system, (2) local lesions of the posterior hypothalamus, and (3) endocrine obesity, whereas it moves in the opposite direction in (1) local lesions of the anterior hypothalamus, (2) neuro-endocrine obesity with sleep disturbances, (3) ovarian obesity and neuroses of the climacteric, and (4) metabolic-alimentary obesity with functional disturbance of the central nervous system.

The authors found that both the obesity and the EEG changes responded to a low-carbohydrate diet. They started with a diet supplying 2,100 to 2,300 Cal. (carbohydrate 280 to 300 g., fat 50 to 55 g., and protein 100 g.); this was then reduced to one supplying 1,200 Cal. and containing only 100 g. of carbohydrate after a week or 10 days. Normal amounts of vitamins and mineral salts were given. This diet was maintained for 45 days, during which the loss of weight was 28 to 30 kg. The diet may be supplemented with hormone therapy as indicated. Improvement in symptoms, such as those of diabetes insipidus, somnolence, and hypertension, occurred in many of the cases described in this paper.
L. Firman-Edwards

536. **Therapy of Acute, Chronic and Mixed Hepatic Porphyria Patients with Chelating Agents**
H. A. Peters, P. L. Eichman, and H. H. Reese. *Neurology* [*Neurology* (*Minneap.*)] **8**, 621–632, Aug., 1958. 34 refs.

In this paper from the University of Wisconsin Medical School, Madison, the authors summarize the symptoms and signs found in 47 cases of porphyria, of which 32 were of the acute, one of the chronic, and 5 of the mixed hepatic type, while 12, in which the symptoms were suggestive of acute porphyria but porphobilinogenuria was scanty, were designated " paraporphyria ". Chelating agents were used in the treatment of 37 of these patients, dimercaprol (B.A.L.) being given intramuscularly in doses of 50 to 1,200 mg. a day for 4 to 60 days in 26 cases and sodium calciumedetate intravenously in doses of 1 to 10 g. a day for 2 to 5 days (sometimes repeated) in 4 cases, while 7 patients received both drugs. This treatment seemed to be beneficial in 31 of the 37 cases, particularly in those of mixed hepatic porphyria and paraporphyria. *H. Harris*

Gastroenterology

STOMACH AND DUODENUM

537. **Exfoliative Cytology as an Aid to the Diagnosis of Gastric Carcinoma. A Preliminary Analysis of 116 Cases**
E. K. KURT, C. H. BROWN, L. J. MCCORMACK, J. B. HAZARD, and D. BELOVICH. *Cleveland Clinic Quarterly* [*Cleveland Clin. Quart.*] **25**, 113–146, July [received Sept.], 1958. 9 figs., 20 refs.

The authors describe a simple aspiration technique for the examination of exfoliated gastric cells in which a plastic Levin tube is used. The fasting stomach is washed until the aspirate is clear and then 500 ml. of acetate buffer solution is introduced, most of which is afterwards withdrawn into an ice-cold container, slides being prepared after centrifugation. The small residue of fluid in the stomach, relatively rich in cells, is similarly treated.

At the Cleveland Clinic, Ohio, this technique was used on 116 consecutive patients; of these, 37 were subjected to laparotomy, the diagnosis of carcinoma being confirmed in 13 and the presence of benign lesions verified in 21. There was thus a correct cytological diagnosis in 92% of the cases. A false positive result was obtained in 2 cases and a false negative in one. In the remaining 79 cases the negative cytological findings could not be checked as operation was not performed.

The authors admit that the results in this series indicate a trend only, but they suggest that the technique may well be more reliable for the diagnosis of gastric malignancy than radiological or gastroscopic examination, particularly in early cases. They do not, however, recommend it as a routine procedure.

A. Wynn Williams

538. **Gastrointestinal Haemorrhage and Salicylates**
A. S. ALVAREZ and W. H. J. SUMMERSKILL. *Lancet* [*Lancet*] **2**, 920–925, Nov. 1, 1958. 23 refs.

Various authors in recent years have incriminated aspirin (acetylsalicylic acid) as a causal factor in major gastro-intestinal haemorrhage. The present authors therefore report the results of an investigation designed to clarify the relationship between salicylate consumption and gastro-intestinal haemorrhage which was carried out on 103 patients admitted to the Department of Gastroenterology of the Central Middlesex Hospital, London, suffering from haematemesis or melaena thought to be associated with acute or chronic peptic ulceration. A series of 103 consecutive new out-patients who had symptoms of dyspepsia but no gastro-intestinal bleeding and who were identical in regard to sex distribution served as a control group; the average age of the two groups was 55 and 45 years respectively.

Of the patients with haemorrhage, 55 had taken salicylates during the 72 hours preceding the haemorrhage, 49 of them within 24 hours of the haemorrhage, and 35 within 12 hours, whereas in the control group, in striking contrast, 17 patients had taken salicylates within 72 hours of attending hospital, and only 7 within 24 hours of attending hospital. Thus the 24 hours immediately before a haemorrhage appeared to be particularly important. The habitual consumption of salicylates in the two groups was approximately the same. Among the patients with haemorrhage investigation showed that (1) " acute lesions ", that is, either proven acute gastric ulcers or lesions not demonstrable radiologically, were more frequent in the " salicylate-positive " patients with bleeding than in the " salicylate-negative " patients with bleeding; (2) the severity of bleeding was not related to salicylate consumption; and (3) 4 patients had taken a soluble preparation of aspirin before the occurrence of bleeding.

The stools were tested for occult blood during controlled periods in a series of 35 subjects, comprising 14 patients with peptic ulcer, 6 with dyspepsia but no radiologically detectable lesion, and 15 with no evidence of gastro-intestinal disease. When aspirin or soluble aspirin was administered in a dosage of 10 grains (0·7 g.) 4 times daily occult blood loss in the stools occurred in 50% of all 3 groups; it did not occur during periods of medication with phenacetin, " panadol " (N-acetyl-*p*-aminophenol), or " antidol " (salicylamide-[2-ethoxy-ethyl]-ether). These findings are in line with those reported by previous workers. The authors conclude that the results here reported support the evidence for a causal relationship between salicylate consumption and massive gastro-intestinal haemorrhage from peptic ulcer. It is pointed out that 80% of the patients with major haemorrhage after ingestion of salicylate had proven duodenal or chronic gastric ulcer or a history of dyspepsia. The clinical history, together with the findings at emergency partial gastrectomy, indicated that acute erosions in the stomach (and possibly also lower in the gastro-intestinal tract) were sometimes responsible, although activation of a pre-existing chronic peptic ulcer often seemed likely.

[It is apparent from the text that the authors use the term " salicylate " to designate either aspirin or compound preparations containing aspirin. Aspirin is, in fact, the only salicylate which is incriminated by these studies.] *Joseph Parness*

539. **Acute Peptic Ulceration in Emphysema**
F. J. FLINT and A. J. N. WARRACK. *Lancet* [*Lancet*] **2**, 178–179, July 26, 1958. 9 refs.

The demonstration at necropsy of a high incidence of peptic ulcer among subjects with emphysema, with or without cor pulmonale, has recently been reported by several authors. Similar results were obtained from an analysis of the findings in a series of 88 subjects with

congestive heart failure who were examined post mortem in the course of one year at the City General Hospital, Sheffield.

Out of 24 subjects in whom the diagnosis was cor pulmonale, 10 were found to have one or more peptic ulcers—acute (usually multiple) in 5, chronic in 3, and combined in 2. In contrast, peptic ulceration was found in only 3 of the 64 subjects with other types of heart failure, and in all these cases the ulceration was chronic. In view of these findings a special search was made for acute peptic ulcers at all post-mortem examinations over a 2-year period. Such ulcers were found in 18 (21%) of the 87 subjects with diffuse emphysema and in 17 (2%) of the remaining 1,037 subjects examined. Among 53 emphysematous subjects with cor pulmonale, 13 (25%) had one or more acute ulcers. Evidence of bleeding was found at necropsy in 8 of the 18 cases of ulceration associated with emphysema and during life in 3 others; in one case the ulcer had perforated. None of the 18 patients had complained of dyspepsia. The ulceration was usually multiple and situated in the antrum.

The authors suggest that the association of peptic ulceration with severe emphysema may possibly be due to the derangement of the gaseous equilibrium of the blood. *Richard Doll*

540. **Bronchitis, Aspirin, Smoking and Other Factors in the Aetiology of Peptic Ulcer**
A. ALLIBONE and F. J. FLINT. *Lancet* [*Lancet*] **2**, 179–182, July 26, 1958. 17 refs.

In an attempt to assess the significance of various factors in the aetiology of peptic ulcer the authors determined the frequency of their occurrence in a series of 129 patients admitted to the City General Hospital, Sheffield, for gastro-intestinal haemorrhage (100) or for a perforated ulcer (29) and compared it with that found in a control series. The control subjects were chosen from among the patients admitted to the same hospital for other non-thoracic surgical emergencies or accidental injuries, each patient in the former series being paired with a control subject of the same sex and within the same 5-year age group who was admitted to hospital within the same 2-week period. Patients in both series were questioned in a standard way, both members of each pair being questioned by the same interrogator.

No significant differences were found in the numbers of patients in the two series who (*a*) had had an acute respiratory infection within the previous 4 weeks (53 in the study series against 42 in the control series), (*b*) had suffered from chronic bronchitis with or without heart failure (19 against 29), (*c*) had taken aspirin within the previous 2 weeks (61 against 59), or (*d*) had taken alcohol (50 against 51) or various other drugs within the previous 2 weeks. The frequency of severe "mental stress" during the 4 weeks before admission was also similar in the two series. Inquiries about smoking habits were made only of the last 207 pairs of patients; among the males a significant difference ($P<1\%$) was found between the numbers who habitually smoked cigarettes at the time of their illness—58 of the 76 in the study series and 42 of the 76 in the control series.

It is concluded that the high prevalence of acute peptic ulcer which has been found at necropsy among patients with emphysema and cor pulmonale [see Abstract 539] cannot be attributed to an association of ulceration with uncomplicated chronic bronchitis or with acute respiratory infections. *Richard Doll*

541. **The Basophilic Substance of the Gastric Chief Cells and Its Relation to the Process of Secretion.** [Monograph, in English]
J. WEBER. *Acta anatomica* [*Acta anat.* (*Basel*)] **33**, Suppl. 31, 1–79, 1958. 30 figs., bibliography.

LIVER

542. **Serum *iso*Citric Dehydrogenase Activity with Particular Reference to Liver Disease**
R. L. STERKEL, J. A. SPENCER, S. K. WOLFSON, and H. G. WILLIAMS-ASHMAN. *Journal of Laboratory and Clinical Medicine* [*J. Lab. clin. Med.*] **52**, 176–184, Aug., 1958. 5 figs., 18 refs.

The triphosphopyridine nucleotide-specific enzyme *iso*citric dehydrogenase (I.C.D.) is a further example of an enzyme system which undergoes change in hepatic disease and the estimation of which may therefore be of value in the diagnosis of such disease. The authors, working at the University of Chicago, found that serum I.C.D. activity increased from the normal range of 47 to 264 units per ml. to a mean of 1,480 units per ml. in acute infective hepatitis. Lesser rises were seen in patients with hepatic metastases from neoplasms elsewhere. No increase was observed in cases of portal cirrhosis or extrahepatic obstructive jaundice.

The activity of the enzyme glutamic pyruvic transaminase, which was assayed simultaneously, showed similar responses, but it was also increased in cases of extrahepatic obstructive jaundice, so that determination of I.C.D. activity is of greater value in differentiating between intra- and extra-hepatic biliary obstruction. No rise in the serum I.C.D. level was observed in patients with myocardial infarction, despite the high concentration of this enzyme in cardiac muscle. Normal values were also obtained in a wide variety of other diseases, including neoplastic disease, Cushing's syndrome, viral pneumonia, pulmonary tuberculosis, diabetes, acute rheumatoid arthritis, and ulcerative colitis. *M. Sandler*

543. **Chlorothiazide in Liver Disease.** (Le chlorothiazide dans les affections hépatiques)
A. E. READ, J. L. LAIDLAW, R. HASLAM, and S. SHERLOCK. *Archives des maladies de l'appareil digestif et des maladies de la nutrition* [*Arch. Mal. Appar. dig.*] **47**, 937–947, Sept., 1958. 8 figs.

In this paper from the Postgraduate Medical School of London studies of the therapeutic effect of chlorothiazide in cases of hepatic cirrhosis with ascites are reported. Administration of the drug in doses of 500 mg. 6-hourly to 5 patients, all of whom were receiving a low-sodium diet, was followed by a satisfactory diuresis in only 2 cases, but in all 5 there was a heavy loss of

potassium in the urine and a fall in the serum potassium level. Urinary sodium excretion was unchanged or increased. In some cases symptoms and electrocardiographic evidence of potassium deficiency were noted, and similar effects of chlorothiazide administration have been observed in cases of cirrhosis without ascites and in healthy subjects.

In some patients who had previously experienced hepatic coma or pre-coma definite neuropsychiatric and electroencephalographic changes typical of potassium deficiency developed on administration of the drug. These, however, disappeared when potassium was given, even if chlorothiazide was continued.

It is concluded that if chlorothiazide is being given as a diuretic in the treatment of cirrhosis with ascites adequate potassium must also be administered. With this precaution, and with intermittent administration, the drug may prove useful in such cases. *J. W. McNee*

544. **Subacute Hepatic Necrosis and Postnecrotic Cirrhosis Due to Anicteric Infections with the Hepatitis Virus**
G. KLATSKIN. *American Journal of Medicine* [*Amer. J. Med.*] **25**, 333–358, Sept., 1958. 20 figs., 45 refs.

In this paper from Yale University School of Medicine, New Haven, Connecticut, a study is reported of 9 cases (out of a total of 69) of post-necrotic cirrhosis of the liver in which there was good reason to believe that the illness followed anicteric viral hepatitis. The onset was fairly abrupt and there was no evidence of exposure to alcohol or toxic drugs or of jaundice during the first 3 months. Liver biopsy specimens obtained early in the course of the disease were characteristic of subacute hepatic necrosis. Jaundice, hepatomegaly, or ascites appeared 2 to 18 months after the onset of symptoms. Of the 9 patients, 5 died in hepatic coma during the period of observation. In one case a remission was induced with steroid therapy, but otherwise the course of the disease was not obviously influenced by any form of treatment. All except one of the patients were females over the age of 40. No clinical or biochemical features were observed which would permit this syndrome to be distinguished with certainty from other forms of cirrhosis of the liver.

P. C. Reynell

545. **A Controlled Study of the Effects of L-Arginine on Hepatic Encephalopathy**
T. B. REYNOLDS, A. D. REDEKER, and P. DAVIS. *American Journal of Medicine* [*Amer. J. Med.*] **25**, 359–367, Sept., 1958. 3 figs., 19 refs.

A double-blind controlled trial of L-arginine in " hepatic encephalopathy " was carried out on 32 patients at Los Angeles County Hospital. The effect of an intravenous infusion of 30 g. of L-arginine in 500 ml. of water was compared with that of 500 ml. of 5% dextrose, a total of 60 infusions being given to the 32 patients, 29 of whom had cirrhosis of the liver. Arterial blood ammonium levels were determined before and after each infusion.

No significant difference was observed between the solutions in their effects on the clinical status or the blood ammonium levels.

[It is to be hoped that every new agent introduced for the treatment of hepatic coma will be subjected to a careful controlled trial of this kind as soon as possible; otherwise the disillusionment is apt to last for years.]

P. C. Reynell

546. **Hepatic Fibrosis: Pathways and Mechanism.** [Review Article]
H. POPPER, F. HUTTERER, G. KENT, H. M. VAN DER NOEN, F. PARENETTO, F. SCHAFFNER, E. J. SINGER, and F. G. ZAK. *Journal of the Mount Sinai Hospital* [*J. Mt Sinai Hosp.*] **25**, 378–390, Sept.–Oct., 1958. 6 figs., 34 refs.

PANCREAS

547. **Leucine Aminopeptidase Activity. Observations in Patients with Cancer of the Pancreas and Other Diseases**
A. M. RUTENBURG, J. A. GOLDBARG, and E. P. PINEDA. *New England Journal of Medicine* [*New Engl. J. Med.*] **259**, 469–472, Sept. 4, 1958. 2 figs., 6 refs.

At Beth Israel Hospital (Harvard Medical School), Boston, the authors have determined the level of leucine aminopeptidase activity in the serum of 300 and in the urine of 200 patients with a variety of conditions, as well as in a control group of healthy subjects. They found greatly increased serum values (an average of 20 standard deviations above the normal mean) in all of 14 patients with carcinoma of the head of the pancreas, including 2 without symptoms, and this held true even in the absence of jaundice or a raised serum alkaline-phosphatase level. In 82 consecutive patients with carcinoma not involving the pancreas or liver the serum enzyme levels were normal, but 6 out of 12 with extensive liver metastases showed an increase, which however did not as a rule attain the heights found in the patients with carcinoma of the pancreas. In 2 cases of carcinoma of the tail of the pancreas there were also liver metastases and the cause of the elevation in these was therefore doubtful. Raised serum enzyme levels were also found in 3 patients with secondary involvement of the pancreas from a primary growth in the stomach or ovary and one with malignant lymphoma involving the pancreas. Moderately increased serum levels also occurred in patients with acute pancreatitis and choledocholithiasis, but were not constant. Results in cases of primary liver disease [not reported in detail] are stated to have been " generally significantly lower than those in patients with cancer of the head of the pancreas ".

While the levels of leucine aminopeptidase in the urine were also greatly increased in cases of carcinoma of the head of the pancreas, similar elevations occurred in other conditions, including Hodgkin's disease, malignant lymphoma, leukaemia, and multiple myeloma, and also in about half the cases of cancer arising at sites other than the pancreas. The authors conclude that the determination of leucine aminopeptidase activity in the serum and urine appears to be of value in the early diagnosis of carcinoma of the head of the pancreas and that in particular the finding of normal values may be considered definitely to rule out such a diagnosis.

B. F. Swynnerton

Cardiovascular System

548. **The Conservative Management of Heart Disease Complicating Pregnancy**
W. S. SMITH and P. B. B. GATENBY. *Irish Journal of Medical Science* [*Irish J. med. Sci.*] **6**, 457–466, Oct., 1958. 2 figs., 5 refs.

The authors review the results over the period 1949–57 of the conservative management of heart disease complicating pregnancy in patients delivered at the Rotunda Hospital, Dublin, where therapeutic abortion and sterilization are not used. Few of these patients practise active birth control and thus many women suffering from heart disease who have borne large families are admitted to the hospital. Of 230 patients with cardiac disease observed during 400 pregnancies, 218 suffered from rheumatic heart disease, 6 from congenital heart disease, 3 from subacute bacterial endocarditis, 2 from coronary heart disease, and one from auricular fibrillation of obscure origin.

There were 8 maternal deaths in all (mortality 2%), 7 occurring in patients with mitral stenosis and the other in a patient in the terminal stages of coronary disease. One patient had eclampsia, 3 were in the terminal stages of rheumatic heart disease, while pneumonia was responsible for 2 and probably 3 deaths. The foetal loss amounted to 26 infants, 3 being undelivered, 10 stillborn, and 13 dying in the neonatal period; half of these deaths were due to purely obstetrical causes or foetal malformations incompatible with life, but 7 were due to the mother's cardiac condition and a further 6 (in premature infants) could also possibly be related to it. In only 67 of the 379 pregnancies complicated by rheumatic heart disease was the latter severe (Grade III or IV). Mitral disease was the commonest lesion, 55 of these patients suffering from pure mitral stenosis, and all the deaths occurred in this group.

After diagnosis of the cardiac condition all patients except those in Grade I were seen by both a physician and an obstetrician every 2 weeks until the 32nd week of pregnancy, and thereafter every week until admission, watch being kept especially for signs of pulmonary basal congestion, bronchitis, haemoptysis, or increasing breathlessness; at the onset of any of these signs they were admitted to hospital for rest, digitalization, and correction of respiratory infections and anaemia. Most of the deliveries took place in hospital, but 35 were carried out at home for various reasons. Caesarean section was performed on 7 primigravidae and 11 multigravidae, in 5 of these because of the cardiac condition and in 2 for obstetrical reasons. The authors stress the latent anaemia present in these cases, as this often appeared to be the factor precipitating cardiac failure. None of the 12 patients with auricular fibrillation died, though 3 developed cardiac failure in pregnancy. There were 21 instances of gross cardiac failure, 7 of which occurred in the puerperium and 3 of which proved fatal. All 13 patients with pulmonary congestion recovered, though one died 6 weeks after confinement, and all 21 who developed bronchitis recovered. The authors were unable to confirm a suggestion that cardiac failure is especially liable to occur about the 32nd week. In 22 cases of mitral stenosis observed through 3 or more pregnancies it appeared that a parity above 4 was a factor causing deterioration of the cardiac state in pregnancy. *R. Wyburn-Mason*

549. **The Pure Form of Thyrotoxic Heart Disease. A Clinical and Pathological Study**
P. SCHLESINGER and A. B. BENCHIMOL. *American Journal of Cardiology* [*Amer. J. Cardiol.*] **2**, 430–440, Oct., 1958. 8 figs., 36 refs.

In this paper from the Fifth Medical Clinic, University of Brazil, and the Hospital dos Servidores do Estado, Rio de Janeiro, 4 cases of thyrotoxic heart disease are described. Congestive cardiac failure was present in 3 of them and left ventricular hypertrophy without congestive failure in one.

The first patient, a 36-year-old negress who had had thyrotoxicosis for 2 years, was admitted to hospital with cardiomegaly, recent congestive heart failure, and regular cardiac rhythm. After treatment with digitalis and diuretics all signs and symptoms of cardiac failure disappeared and the heart rapidly became normal in size. A prolonged course of antithyroid drugs was then given and subtotal thyroidectomy was carried out after an interval of 18 months. The second patient, a female aged 44 years, had recent thyrotoxicosis accompanied by congestive failure and paroxysmal auricular fibrillation. To control the heart failure digitalis and diuretics had to be given in addition to an antithyroid drug, the last-named being ineffective alone. Following thyroidectomy, which was performed 10 weeks after admission, all signs and symptoms of cardiac failure disappeared, although medication had been discontinued. The third patient, a 39-year-old negress, had had thyrotoxicosis for 18 months and congestive failure with auricular fibrillation for 6 months. Digitalis and diuretics failed to control the cardiovascular state until an aqueous solution of iodine was given in addition. The patient died 8 days after admission from a probable pulmonary embolism. At necropsy cardiac hypertrophy and interstitial myocarditis were found. The fourth patient, a female aged 40 years, had thyrotoxicosis and, on radiological examination, uncomplicated cardiomegaly. She died suddenly after subtotal thyroidectomy, which was carried out 2 weeks after admission. Necropsy revealed cardiac hypertrophy but no histological changes.

In view of the reversibility of the cardiovascular changes after treatment of the thyrotoxicosis, the absence of any possible aetiological factor other than thyrotoxicosis, and the histopathological changes in one case, the authors conclude that heart disease solely attributable to thyrotoxicosis is a disease entity. *Gerald Sandler*

550. **The Nature and Distribution of Cardiac Edema**
J. R. JAENIKE and C. WATERHOUSE. *Journal of Laboratory and Clinical Medicine* [*J. Lab. clin. Med.*] **52**, 384–393, Sept., 1958. 21 refs.

Writing from the University of Rochester School of Medicine, New York, the authors state that "a clear exposition of the abnormalities in water and electrolyte metabolism associated with congestive heart failure is essential to a further understanding of the pathogenesis of cardiac oedema". In this paper they report their observations on water and electrolyte balance and on the chloride and deuterium spaces in 6 patients with congestive heart failure during the period when these subjects were losing their oedema as a result of rest or diuretic treatment. The fluid lost externally could be accounted for mainly by diminution in the extracellular fluid and sodium and chloride were lost in the proportions present in that fluid. The administration of diuretic agents, in association with low potassium intake, led to negative potassium balance during treatment. On a few occasions the observed loss of cation was smaller than the loss calculated from the measured concentration of the cation; the explanation offered for this is that some base had become "inactivated", that is, had assumed a state in which it did not contribute to the osmolarity of the fluid containing it. They conclude that the essential primary abnormality of fluid and electrolyte metabolism in patients in heart failure is the accumulation of excessive intravascular and interstitial fluid as a result of renal retention of salt and water.

[It is perhaps pertinent to point out that other workers, notably Wynn and Edelman, have failed to find evidence of cation inactivation in other circumstances of rapid change in the body fluid.] *D. A. K. Black*

DIAGNOSTIC METHODS

551. **The Electrocardiographic Recognition of Ventricular Hypertrophy in Congenital Cardiovascular Disease during the First Year of Life**
J. S. OLDHAM. *Archives of Disease in Childhood* [*Arch. Dis. Childh.*] **33**, 346–349, Aug., 1958. 10 refs.

The value of the electrocardiogram (ECG) in the diagnosis of ventricular hypertrophy in infants with severe congenital cardiovascular abnormalities was studied at the Children's and Dudley Road Hospitals, Birmingham, in a series of 40 cases in which the nature of the cardiac lesions was confirmed at necropsy. Tracings were obtained at ages ranging from 2 days to 11 months, and within 2 months of death in all but 2 cases. The R deflection was regarded as abnormal if it exceeded the 99·5 percentile maximum for age, and the intrinsicoid deflection in V1 was considered to be delayed if it occurred 0·04 second or more after the beginning of the QRS complex. The presence of ventricular hypertrophy was confirmed at necropsy in every case, being confined to the right side in 20 cases and to the left in 3, the remaining 17 hearts showing combined ventricular hypertrophy.

One or other of the abnormalities defined above was present in Lead V1 in only 11 (65%) of 17 cases of isolated right ventricular hypertrophy (3 cases with evidence of extreme clockwise rotation being excluded) and in 13 (75%) of 17 cases of combined ventricular hypertrophy. As criteria for the ECG recognition of right ventricular hypertrophy these abnormalities may therefore be inadequate at this age. In a high proportion of the cases of isolated right ventricular hypertrophy, however, the ventricular complex was of abnormal configuration. Thus it might show a solitary R followed by an upright T wave, or there might be an initial q deflection. These abnormal patterns were not found in cases of combined ventricular hypertrophy. Excessive amplitude of R in Lead V6 was of some help in detecting the presence of left-sided enlargement, being present in one of the 3 cases of left ventricular hypertrophy and in 6 of the 17 cases of combined hypertrophy, but delay of the intrinsicoid deflection in this lead was not found useful for this purpose. In Lead VR a QR or R pattern was found only in cases of isolated right ventricular hypertrophy, but when present was usually associated with an R or Rq pattern in Lead V1. In 2 cases, however, a QR pattern in Lead VR was associated with an Rs complex in Lead V1, and in such cases Lead VR may help in distinguishing between isolated right and combined ventricular hypertrophy. In about 50% of cases of combined ventricular hypertrophy the ECG provided evidence of right ventricular hypertrophy alone. *R. S. Stevens*

552. **The Electrocardiogram in Cor Pulmonale Secondary to Pulmonary Emphysema: a Study of 18 Cases Proved by Autopsy**
R. W. PHILLIPS. *American Heart Journal* [*Amer. Heart J.*] **56**, 352–371, Sept., 1958. 4 figs., 24 refs.

An analysis of the 12-lead electrocardiograms (ECGs) of 18 consecutive patients dying at the Veterans Administration Hospital, Providence, Rhode Island, with chronic cor pulmonale secondary to pulmonary emphysema, proved by necropsy, is reported. Particular attention was paid to those findings which are generally regarded as helpful in the diagnosis of cor pulmonale, namely, P pulmonale and signs of right ventricular hypertrophy. The former was defined as a P wave greater than 2·5 mm. in height in Lead II, III, or aV_F. For evaluating the latter several sets of criteria were used, namely, those of Sokolow and Lyon (*Amer. Heart J.*, 1949, **38**, 273), Grishman *et al.* (ibid., 1955, **50**, 591), Milnor (*Circulation*, 1957, **16**, 348), and Scott *et al.* (ibid, 1955, **11**, 927).

Evidence of P pulmonale was found in 4 cases (22%). The incidence of signs of right ventricular hypertrophy varied with the criteria employed. According to those of Scott *et al.* and Grishman *et al.* they were present in 7 cases (38%), whereas according to those of Sokolow and Lyon and of Milnor they were present in the same 7 cases and in 6 others, making 13 (72%) altogether. Correlation with the necropsy findings showed that of the 10 cases in which the heart weighed less than 500 g., 5 had ECG evidence of right ventricular hypertrophy according to the criteria of Sokolow and Lyon and of Milnor and only one according to those of the other authorities, while in 5 cases none of the 4 sets of criteria were satisfied. It would appear from these findings that

those ECG signs which depend predominantly on the orientation of the major electrical forces in an anterior direction detect only an advanced degree of hypertrophy.

In 4 cases serial tracings were available, and from a study of these it is concluded that the development of the ECG pattern of cor pulmonale takes place in three stages. In the first the ECG is normal, with the major electrical forces directed to the left and posteriorly. In the second the direction of these forces is to the right in the frontal plane but still posterior—that is, right axis deviation is present, with deep S waves in the left precordial leads, but a prominent R wave is not seen in the right precordial leads. The third and final stage is characterized by deviation of the electrical axis anteriorly as well as to the right. *A. Schott*

553. **Accidental Hypothermia. A Common Condition with a Pathognomonic Electrocardiogram**
D. EMSLIE-SMITH. *Lancet* [*Lancet*] **2**, 492–495, Sept. 6, 1958. 3 figs., 12 refs.

Accidental hypothermia has recently been diagnosed nine times in elderly patients in circumstances which suggest that it is much commoner than is generally supposed. The electrocardiogram showed a pattern pathognomonic of hypothermia in 7 of the 8 cases in which it was recorded: in the eighth case the typical features were masked by bundle-branch block.

The RR, PR, QRS, and QTC intervals were lengthened. The characteristic J deflection of hypothermia was present in leads related to the left ventricle; when it was conspicuous, T was sometimes inverted. In other leads the base of QRS was widened. These changes were identical with those constantly seen in induced hypothermia in patients with normal hearts and analogous to those found in experimental hypothermia in dogs.

Failure to use adequate leads, especially left chest leads, probably explains why this pathognomonic pattern has not been constantly found in accidental hypothermia.—[Author's summary.]

CONGENITAL HEART DISEASE

554. **The Eisenmenger Syndrome or Pulmonary Hypertension with Reversed Central Shunt**
P. WOOD. *British Medical Journal* [*Brit. med. J.*] **2**, 701–709, Sept. 20, and 755–762, Sept. 27, 1958. 24 figs., bibliography.

In this paper (which is the text of the Croonian Lectures for 1958) the author suggests that the condition of which a typical example was first described by Eisenmenger in 1897 and which has since become known as Eisenmenger's complex can be redefined in the light of modern knowledge as "pulmonary hypertension at systemic level, due to a high pulmonary vascular resistance (over 800 dynes per second per cm.^{5}), with reversed or bidirectional shunt through a large ventricular septal defect (1·5 to 3 cm. across)". He defends the retention of the eponym for this condition, but points out that "a remarkably similar physiological situation occurs when any large communication between the two circulations is complicated by a pulmonary vascular resistance around systemic level" and lists 12 different types of anatomical abnormality which may present in this way. Since the exact anatomical diagnosis in such cases may be uncertain, he has previously suggested (*Diseases of the Heart and Circulation*, London, 1956) that the term "Eisenmenger's syndrome" be used to embrace all of this group of conditions "when behaving physiologically like 'Eisenmenger's complex' proper". He now elaborates this theme and describes the distinctive characteristics of the members of the group on the basis of an analysis of 127 cases of Eisenmenger's syndrome personally investigated, of which 15 came to necropsy, together with 38 cases collected from other sources, all of which were examined post mortem.

Of the various abnormalities with which Eisenmenger's syndrome may be associated the commonest are patent ductus arteriosus, ventricular septal defect, and atrial septal defect. Patients with atrial septal defect generally develop the syndrome, if at all, in adult life, the syndrome presenting at an average age of 35 years. Their high pulmonary resistance is apparently acquired and is by no means inevitable, for the pulmonary resistance usually remains low in spite of a lifelong heavy pulmonary flow. In contrast, patients with large interventricular and aorto-pulmonary communications usually develop the Eisenmenger syndrome early in life, for the right ventricle and pulmonary artery are inescapably exposed to systemic pressure. Their high pulmonary resistance is established at birth or in infancy.

The chief symptoms of the syndrome are effort dyspnoea (which may, however, be minimal), angina pectoris, syncope, haemoptysis, and ultimately congestive failure. The physical signs include cyanosis and finger clubbing, polycythaemia, and pulmonary hypertension, perhaps with pulmonary or tricuspid valvular incompetence. The electrocardiogram is usually that of right ventricular hypertrophy; P waves may be tall and arrhythmias are uncommon. The radiograph of the chest shows cardiac enlargement mainly affecting the right ventricle and dilatation of the pulmonary trunk and main arteries, with an oligaemic appearance in the lung periphery. Accurate diagnosis of the underlying anatomical abnormality is difficult, even after full investigation. The frequency of these clinical features in the various types of case in the author's series is reviewed, as are the results of catheterization, angiocardiography, and dye-dilution studies.

Among the 53 cases in which necropsy was performed death was due to haemoptysis in 29%, attempted surgical cure in 26%, congestive failure in 17%, and presumed ventricular fibrillation in 14%. The size of communication in cases of patent ductus arteriosus and ventricular septal defect was large compared with that usually found in similar cases without Eisenmenger's syndrome, whereas in cases of atrial septal defect it was no bigger than in cases with a normal or low pulmonary vascular resistance. The histological changes in the pulmonary vessels are briefly described, and the protective effect of pulmonary stenosis is noted. Whether or not the aorta overrides the right ventricle is considered to be unimportant for the genesis of the syndrome.

The occurrence of a common physiological pattern in association with so many different types of anatomical defect is explained by the author as follows. In the normal child at birth the pulmonary resistance falls rapidly with the expansion of the lungs with air to a value roughly equal to that of the systemic circulation, its further fall to adult level being a gradual process associated with diminishing vasoconstrictor tone due to rising alveolar oxygen tension, involution of the muscular pulmonary arteries, and closure of the ductus arteriosus. This process is prevented in most cases of Eisenmenger's syndrome by the presence of a large communication which exposes the pulmonary arterial tree to systemic pressure, so that vasoconstrictor tone is maintained and atrophy of the muscular arteries is prevented. But in atrial septal defect no left-to-right shunt occurs for some time after birth so that pulmonary vascular resistance usually falls to normal. In a few cases it remains slightly raised and gradually increases further with the development of internal fibrosis.

Surgical cure should be attempted only when it can be shown that the pulmonary resistance is not grossly raised and that closure of the defect will result in a fall in pulmonary pressure. Vasodilator drugs are useless, and medical treatment should aim at attempting to prevent secondary thrombotic lesions of the pulmonary vessels by means of anticoagulants.

[The essential feature of the Eisenmenger syndrome, the high pulmonary vascular resistance, is convincingly explained by the author, whose closely reasoned argument is supported by a wealth of well presented data. These lectures cannot readily be abstracted and should be read in full.] *J. A. Cosh*

555. **The Aetiology of Pulmonary Thrombosis in Cyanotic Congenital Heart Disease with Pulmonary Stenosis**
D. HEATH, J. W. DUSHANE, E. H. WOOD, and J. E. EDWARDS. *Thorax* [*Thorax*] **13**, 213–217, Sept., 1958. 2 figs., 8 refs.

The relationship of the incidence of pulmonary thrombosis to age, pulmonary arterial blood flow, and haemoglobin level was investigated in 25 patients with pulmonary stenosis, which was associated with a septal defect in all but 2 patients. Pulmonary thrombosis was present when the pulmonary index was less than 2·5 litres per minute per square metre of body surface but was absent when the flow index was normal or increased. In the presence of a ventricular septal defect when the pulmonary blood flow was abnormally high, pulmonary hypertension and the early structural changes of hypertensive pulmonary vascular disease in the form of medial hypertrophy in the muscular pulmonary arteries and arterioles were present. The second factor predisposing to pulmonary thrombosis in patients with low pulmonary blood flows was the increase of blood viscosity due to the compensatory polycythaemia stimulated by the anoxaemia found in such patients.

An indirect relationship exists between pulmonary thrombosis and age, since the pulmonary index tends to decrease with increasing age in patients with pulmonary stenosis, and the factors predisposing to thrombosis have existed for corresponding periods of time and possibly with increased severity. Widespread thrombosis was found in all but 2 of these patients more than 10 years of age; one of these exceptions had a high pulmonary blood flow and hypertensive pulmonary vascular disease and the other had a normal blood flow and only two isolated thrombi. Conversely, only 4 of the 10 patients less than 10 years of age without pulmonary hypertension had pulmonary thrombi; in 3 of these, the pulmonary flow index was 2·2 or less.

The "tetralogy of Fallot", while denoting a precise anatomical entity, has no specific functional significance, and an alternative nomenclature is supported.—[Authors' summary.]

556. **Ebstein's Anomaly. Complete Review of 108 Cases**
J. B. VACCA, D. W. BUSSMANN, and J. G. MUDD. *American Journal of Cardiology* [*Amer. J. Cardiol.*] **2**, 210–226, Aug., 1958. 7 figs., bibliography.

CHRONIC VALVULAR DISEASE

557. **Brucellosis and Heart Disease. III. Chronic Valvular Heart Disease following Nonfatal Brucellosis**
T. M. PEERY and J. M. EVANS. *Annals of Internal Medicine* [*Ann. intern. Med.*] **49**, 568–579, Sept., 1958. 22 refs.

In a previous paper (*J. Amer. med. Ass.*, 1958, **166**, 1123; *Abstr. Wld Med.*, 1958, **24**, 268) Peery discussed the aetiology of calcific aortic stenosis. This further paper from the George Washington University School of Medicine, Washington, D.C., opens with a review of the literature dealing with chronic valvular heart disease resulting from non-fatal brucellosis, and this is followed by 10 case reports which show that endocarditis caused by brucellosis is not necessarily fatal in the acute phase, but tends to heal. It is suggested that these cases support the view that the endocarditis of brucellosis may lead to calcific aortic stenosis. Of the 10 cases described, 4 presented as cases of aortic stenosis and inquiry revealed a history of an illness which had been diagnosed as brucellosis. The other 6 cases were discovered by studying a number of patients in whom brucellosis had been diagnosed previously; in 5 of these the aortic valve was affected and in one the mitral valve. In no case had the *Brucella* organism been isolated.

[The evidence that the brucellosis was the cause of the heart disease in these cases is not very convincing.] *C. Bruce Perry*

558. **Tricuspid Regurgitation Masquerading as Mitral Regurgitation in Patients with Pure Mitral Stenosis**
J. F. URICCHIO, L. BENTIVOGLIO, R. GILMAN, and W. LIKOFF. *American Journal of Medicine* [*Amer. J. Med.*] **25**, 224–230, Aug., 1958. 7 figs., 5 refs.

In this communication from Hahnemann Medical College Hospital and the Bailey Thoracic Clinic, Philadelphia, the authors discuss the clinical aspects and haemodynamics of tricuspid regurgitation mistakenly

diagnosed as mitral regurgitation in patients with pure mitral stenosis, an error which may easily occur when there is marked right ventricular hypertrophy with clockwise rotation of the heart and extension of the tricuspid murmur toward the apex. In 5 cases of this condition, in addition to the typical murmur of mitral stenosis, a loud, harsh, systolic murmur was heard at the apex of the heart, its intensity being highest at the lower left sternal border and at the xiphoid process, and transmitted mainly towards the axilla or sometimes towards the base of the heart. In all cases the electrocardiogram was characteristic of right ventricular hypertrophy, while cardioscopy revealed that the right ventricle and right atrium were enlarged, but never the left ventricle. The most useful examination was ventriculography, which revealed a reflux of dye across the tricuspid orifice. The association of pure mitral stenosis and tricuspid regurgitation was found in every patient at the time of surgical exploration.

The diagnosis is suggested by a history of right ventricular failure persisting for an unusually long period and a systolic murmur loudest at the lower left sternal border and xiphoid process and fading at the apex and axillary area, the murmur becoming less intense when cardiac status improves. The authors stress that the diagnosis of tricuspid insufficiency can be definitely established by ventriculography, and point out that a correct diagnosis will obviate the grave mistake of refusing mitral valvotomy in cases in which it is clearly indicated. *A. I. Suchett-Kaye*

559. **The Surgical Treatment of Mitral Insufficiency.** (Хирургическое лечение митральной недостаточности)

A. N. Bakulev, S. A. Kolesnikov, and Ju. A. Galuško. *Клиническая Медицина* [*Klin. Med.* (*Mosk.*)] **36**, 25–32, No. 8, Aug., 1958. 3 figs., 11 refs.

Before operative treatment is undertaken for mitral insufficiency an accurate diagnosis and quantitative assessment must be made. Pure mitral incompetence and stenosis are comparatively rare; usually some degree of both is present in varying proportions. The usually accepted clinical signs are not always reliable; thus the mere presence of an apical systolic murmur does not necessarily imply a predominant mitral incompetence, even when combined with enlargement of the left ventricle. The present authors cite seven features which they regard as diagnostic of mitral incompetence: (1) a blowing apical systolic murmur conducted to the left axilla; (2) dilatation of the left ventricle; (3) fluoroscopic evidence of regurgitation—the "beam-engine" contour with posterior displacement of the oesophagus at the greater arc; (4) little or no congestion of the lung fields; (5) little or no pulsation of the pulmonary artery; (6) a rise in the left atrial pressure curve (obtained by direct puncture) at the moment of ventricular systole; and (7) a "dynamocardiogram" of characteristic type.

The operation developed by the authors at the Institute of Thoracic Surgery of the Academy of Medicine of the U.S.S.R., Moscow, involves the usual thoracic incision. The left auricular appendix is clamped and opened and the mitral orifice and valve explored with the finger. The surgeon then passes the point of a long curved needle mounted on a handle (like an aneurysm needle but less sharply curved) through an avascular area of the antero-lateral wall of the left ventricle. Guided by the left index finger inserted in the left auricle the needle is then passed upwards to pierce the left posterior part of the fibrous mitral ring and emerge through the wall of the left atrium at the base of the appendix, but posterior to it. An assistant threads a stout silk suture through the eye of the needle, which is then withdrawn into the ventricular cavity and again pushed upwards, but this time through the left anterior part of the mitral ring and out through the atrial wall near to, but slightly below, the first puncture. The two ends of the suture are now secured, the needle withdrawn from the heart, and the suture tied over a "washer" of cartilage, the degree of closure of the mitral ring being controlled by the surgeon's finger, which is then withdrawn and the appendicular incision closed.

After experiments on cadavers and laboratory animals this technique has been used in the treatment of 3 patients so far. The immediate results have been satisfactory, with disappearance of the apical systolic murmur, though in one case a short presystolic murmur and a short proto-diastolic bruit developed after the operation. *L. Firman-Edwards*

560. **Experiences with the Davila–Glover Purse-string Suture in the Correction of Mitral Insufficiency: a Critical Appraisal**

E. M. Kent, W. B. Ford, J. F. Neville, and D. L. Fisher. *Journal of Thoracic Surgery* [*J. thorac. Surg.*] **36**, 421–430, Sept., 1958. 1 fig., 4 refs.

At the Allegheny Hospital (University of Pittsburgh), Pittsburgh, the Davilla–Glover purse-string suture operation for mitral regurgitation has been performed on 30 patients with severe mitral insufficiency. The mortality rate was high and there was a high incidence of recurrence of regurgitation due to "cut-through" of the ligature. There were 13 deaths in hospital, 8 due to uncontrollable ventricular fibrillation at the time of operation, 3 within 24 hours of operation, one from subacute bacterial endocarditis, and one from congestive heart failure. In addition 3 patients died suddenly at home soon after operation in spite of a smooth convalescence. Although in almost every case the regurgitant jet was greatly reduced at the time of operation, it became clear that in some cases this was due to the poor contraction of the left ventricle at the time that the observation was made. A systolic murmur recurred in 7 out of 11 patients who survived for a reasonable time following operation. At necropsy on 3 patients who survived 3 or more months it was found that the purse-string suture had completely cut through and lay free in the atrium in 2 cases and had partially cut through in the third case.

(In the discussion that followed the reading of this paper Davilla emphasized the importance of avoiding the inclusion of any epicardium under the knot of the purse-

string suture, and mentioned that among the last 21 cases in which he had performed this operation there were 6 operative deaths, one late death, and 14 survivors.)

R. L. Hurt

CORONARY DISEASE AND MYOCARDIAL INFARCTION

561. **Iproniazid (Marsilid) in Angina Pectoris**
A. M. MASTER. *American Heart Journal* [*Amer. Heart J.*] **56**, 570–582, Oct., 1958. 2 figs., 18 refs.

The value of iproniazid in the relief of angina was studied in 74 patients, (58 male and 16 female, aged 50 to 70 years). Most of the patients had had up to 20 anginal attacks daily and 6 were in " status anginosus ". Each patient received 50 mg. of iproniazid 3 times a day with 25 mg. of pyridoxine with each dose of iproniazid to minimize side-effects, the duration of treatment being one week to 5 months.

There was complete relief of angina in 13 patients, considerable improvement in 28 patients, " doubtful " change in 3, relief followed by aggravation in one, and no change in 29. The improvement began within 3 to 10 days and lasted up to 2 weeks after the drug was discontinued. Acute coronary insufficiency developed in 3 patients and acute coronary occlusion in 2. Improvement was mainly subjective only, since in a number of patients obtaining relief from angina there was no change in the abnormal electrocardiogram or in the response to exercise tolerance tests. Side-effects included gastro-intestinal disturbances (mainly constipation and dry mouth), disturbances of micturition and impotence, dizziness, hypotension, gain in weight, peripheral neuritis, and cerebral stimulation. In 57 of the patients iproniazid had to be discontinued because of the severity of these side-effects.

The author concludes that iproniazid is a most effective drug for the relief of angina, the effects being due, in part at least, to cerebral stimulation, but that the side-effects limit its therapeutic use.

Gerald Sandler

562. **Coronary and Other Heart Disease in a Group of Irish Males Aged 65–85**
R. M. ACHESON and E. D. ACHESON. *British Journal of Preventive and Social Medicine* [*Brit. J. prev. soc. Med.*] **12**, 147–153, July, 1958. 2 figs., 13 refs.

Because of the rapid increase in mortality from coronary arterial disease during the past 30 years studies of the prevalence of the disease in select communities have topical interest. In an earlier paper (Acheson and Thornton, *Brit. J. prev. Soc. Med.*, 1958, **12**, 82; *Abstr. Wld Med.*, 1958, **24**, 383) it was shown that in the Republic of Ireland the number of deaths certified as due to coronary disease increased 30-fold between 1926 and 1956. The present paper from Trinity College, Dublin, reports a study of the prevalence of the disease in a group of 129 elderly male pensioners (aged 65 to 85), who had all been employed for at least 35 years in a Dublin brewery. It is pointed out that for various reasons these men could not be regarded as representative of the male Dublin population of these ages. All the men were examined by one of the authors, the diagnosis of coronary arterial disease being based on electrocardiographic evidence supported by a clinical history of angina pectoris and the findings on physical examination, which included exercise tolerance tests whenever possible.

No significant difference was found in the range and distribution of blood-pressure readings between men aged 65 to 74 and those aged 75 to 85. [It would have been of interest to compare the readings in men with a firm diagnosis of coronary disease with those in the remainder.] Definite evidence of coronary disease was found in 20% of subjects, while in a further 21% there were abnormal electrocardiographic signs not specific to coronary disease, but considered to be at least partly due to that cause. Only 13% could be definitely classified as not suffering from coronary disease, the diagnosis in the remaining 46% (59 subjects) being regarded as " indeterminate " because of inability to perform exercise tolerance tests for reasons other than angina, inadequate testing, or the presence of electrocardiographic abnormalities of dubious significance.

The relation between these results and those of other workers is discussed, particular reference being made to their similarity to the prevalence rates found in South Wales—38% in miners and 21% in non-miners—by Thomas *et al.* (*Lancet*, 1956, **1**, 414 and 1958, **2**, 540; *Abstr. Wld Med.*, 1956, **20**, 239 and 1959, **25**, 27).

E. Lewis-Faning

563. **Anastomosis in the Coronary Circulation**
W. LAURIE and J. D. WOODS. *Lancet* [*Lancet*] **2**, 812–816, Oct. 18, 1958. 4 figs., 11 refs.

In an attempt to determine whether or not there are functional anastomoses between the coronary arteries and whether, as has been suggested, these increase with age, the authors, at the Edendale Hospital, Natal, examined normal and diseased hearts from Bantu patients. In all 200 hearts were examined, 150 of which proved suitable for study. (An addendum states that the total number of hearts was finally 350 and that the further work supported the findings reported here.) The procedure consisted in the injection of one coronary artery with a gelatin suspension containing lead phosphate. This radio-opaque mass was about seven times more viscid than heparinized blood, and the particle size of the lead phosphate was not less than 35 μ, so that none of the material should have passed the capillaries. With the heart immersed in saline at 45° C. one coronary artery was injected at a pressure of 150 mm. Hg for 20 minutes. The heart was then cooled until the injection mass hardened. The heart was " unrolled " by Schlesinger's technique and radiographs obtained of the coronary circulation. No difference in the anastomoses was observed whether the right or left coronary artery was injected. Some degree of filling of the uninjected artery was seen in 48 out of 87 normal hearts, and in 12 of these filling was complete. Some degree of anastomosis was found in 13 out of 46 healthy subjects under the age of 4 years and in 35 out of 41 over that age. However, of 63 diseased hearts, 40 showed no demonstrable anastomoses.

It is suggested that the majority of healthy people "have a functionally important inherited coronary anastomotic blood-supply [and this] probably protects some against ischaemic heart-disease and may modify ischaemic heart-disease in others". *C. Bruce Perry*

564. **The Degree of Unsaturation of Plasma Lipid Fractions in Coronary Artery Disease**
R. CAREN and L. CORBO. *American Journal of the Medical Sciences* [*Amer. J. med. Sci.*] **236**, 362–368, Sept., 1958. 19 refs.

It has been demonstrated that the feeding of fats containing large amounts of unsaturated fatty acids lowers the serum cholesterol level, perhaps because these fatty acids play some role in the transport of cholesterol. If a deficiency of essential fatty acids is indeed a factor in atherogenesis it could be reasonably expected that a significant difference might be found in the iodine number, that is, the degree of unsaturation, of at least one of the various plasma lipid fractions. At the Cedars of Lebanon Hospital, Los Angeles, therefore, the iodine numbers of the plasma total fatty acids, phospholipid fatty acids, cholesterol ester fatty acids, triglycerides, and the unesterified fatty acids in 8 normal subjects aged 22 to 39 years were compared with those in 7 patients aged 57 to 77 years suffering from proven myocardial infarction. In both groups two subjects were females. No significant difference was found between these two groups, and the authors conclude that "this study does not support the concept that a deficiency of unsaturated (essential) fatty acids is of aetiologic importance in atherosclerosis".

[This is an interesting paper and confirms similar earlier findings. It must be kept in mind, however, that coronary artery disease is the end-product of a long series of pathological processes. Assuming that deficiency of essential fatty acids was a factor in atherogenesis, the absence of significant differences in the iodine numbers of the lipid fractions in healthy young subjects and in old atherosclerotics would not disprove this assumption.]
Z. A. Leitner

565. **Electrophoretic Studies of the Protein Fractions of the Blood in Acute Myocardial Infarction. (Preliminary Communication)** (Значение электрофоретического исследования белковых фракций крови при остром инфаркте миокарда (Предварительное сообщение)
V. M. ZAJCEV. *Терапевтический Архив* [*Ter. Arh.*] **30**, 62–66, No. 9, Sept., 1958. 1 fig., 6 refs.

An electrophoretic study of the blood proteins was carried out on 20 patients, 15 men and 5 women, following acute myocardial infarction caused by coronary arteriosclerosis. The normal proportions of the various protein fractions in the blood are stated to be: albumin 62%, α_1 globulin 4%, α_2 globulin 8%, β globulin 12·5%, and γ globulin 13·5%.

It was found that during the first week after myocardial infarction the albumin fraction was considerably reduced and the ratio of α_2 globulin to β globulin doubled or even more than doubled. During the second and third weeks there was an increase of the β- and γ-globulin fractions. The most significant changes from the point of view not only of diagnosis, but also of prognosis, are considered to be an increase in the α_2:β globulin ratio above unity during the first week accompanied by a fall in the albumin:globulin ratio below unity. *A. Orley*

566. **Prognosis and Treatment of Collapse in Myocardial Infarction.** (Pronostic et traitement du collapsus au cours de l'infarctus du myocarde)
J. HIMBERT, B. BOUMARD, and J. LENÈGRE. *Archives des maladies du cœur et des vaisseaux* [*Arch. Mal. Cœur*] **51**, 728–746, Aug., 1958. Bibliography.

Out of a total of 472 patients with myocardial infarction admitted to the Hôpital Boucicaut, Paris, between January, 1949, and July, 1957, the authors made a special study of 66 who were suffering from collapse of the peripheral circulation and attempted to determine the factors influencing prognosis and to assess the value of modern vasopressor agents, particularly noradrenaline, in treating this complication. The term "collapse" is defined as an arterial systolic pressure of 80 mm. Hg or less occurring during the 4 weeks following the infarction. The series consisted of 55 men and 11 women of an average age of 60·8 (range 43 to 80) years; in 45 of these patients the systolic pressure had fallen to between 50 and 80 mm. and in 21 to less than 50 mm. Hg.

Two patients recovered without specific treatment and the remaining 64 were treated in three groups as follows. (1) In 27 cases the patient was given an intravenous drip infusion of isotonic glucose saline containing 4 mg. of noradrenaline per 500 ml., together with 0·3 g. of dihydroxypropyltheophylline and 50 mg. of heparin, at a rate of 1 to 2 ml. per minute or as required to maintain the blood pressure at about 100 mm. Hg, the duration of treatment varying from 10 minutes to 10 days. (2) In 20 cases phenylephrine (without noradrenaline but with other vasopressor drugs in 6 cases) was given intramuscularly in doses of 5 mg., repeated every 4 to 6 hours according to response. (3) In 17 cases other vasopressor drugs or analeptics, including norephedrine (13 cases), camphor (10), nikethamide (5), and caffeine (2), were given in various combinations.

The over-all mortality was 72·7%. Although the peripheral vascular collapse was reversed in 24 patients, only 16 of these survived. Adverse factors in prognosis were: (1) former hypertension; (2) a previous infarct; (3) secondary collapse (for example, following pulmonary embolism, rupture of the heart, ventricular tachycardia, auriculo-ventricular block, or heparin shock); (4) early onset of collapse (mortality 93·2% on the first day); (5) a systolic pressure lower than 50 mm. Hg (mortality 95·3%); (6) clinically severe shock; and (7) signs of cardiac failure. The survival rates in the three groups were respectively 25·9, 25, and 23·5%. In all cases the important factor appeared to be early treatment, and it was notable that 14 of the 16 survivors were treated within the first hour. The advantages of noradrenaline treatment are detailed, although at the same time the essential need for supporting medication with analgesics, anticoagulants, digitalis, and diuretics is stressed. *V. Reade*

PULMONARY CIRCULATION

567. **Pulmonary Hypertension with Special Reference to the Vasoconstrictive Factor**
P. WOOD. *British Heart Journal* [*Brit. Heart J.*] **20**, 557–570, Oct., 1958. 8 figs., 24 refs.

Writing from the Institute of Cardiology, National Heart Hospital, London, the author classifies pulmonary hypertension into six types, as follows. When pulmonary arterial hypertension is neither (1) the passive reflection of high pulmonary venous pressure nor (2) due to the kinetic effect of excessive flow, increased pulmonary vascular resistance is present. High resistance may be (3) vasoconstrictive (functional), (4) obstructive (due to thrombo-embolism), (5) obliterative (due to reduction of vascular capacity by emphysema or endarteritis fibrosa), or (6) due to some combination of these factors.

The importance of the potentially reversible vasoconstrictive element was investigated in a series of patients with pulmonary hypertension. Acetylcholine was injected directly into the pulmonary artery in order to cause selective pulmonary vasodilatation, which was signified by a fall in pulmonary arterial pressure accompanied by a rise in cardiac output and systemic pressure or, in the case of mitral stenosis, a rise in left atrial pressure. Functional vasoconstriction was demonstrated in 14 out of 16 patients with mitral stenosis, the effect of acetylcholine being greatest where resistance was highest. Permanent intimal obliterative changes were probably present in the 2 cases in which no response occurred; both of these were of long standing. Reversible vasoconstriction was similarly present in 5 out of 6 patients with primary pulmonary hypertension, and in 3 with cor pulmonale (including one example of the Hamman–Rich syndrome). There was no response in a patient with diffuse interstitial fibrosis due to sarcoid. Among 13 patients with the Eisenmenger syndrome, the reversed shunt was interatrial in 6, interventricular in 5, and aorto-pulmonary in 2. Results here were strikingly different, the administration of acetylcholine failing in every instance to cause pulmonary vasodilatation.

It is concluded that pulmonary hypertension accompanying mitral stenosis is an active physiological adjustment rather than a late complication; this accords with the usual clinical history and with the reduction in the hypertension observed after valvotomy. Although organic endarteritis fibrosa can eventually complicate pulmonary hypertension from any cause, functional vasoconstriction may also be basically responsible for primary pulmonary hypertension and is a significant factor in at least some cases of cor pulmonale. The mechanism of the Eisenmenger reaction, however, remains obscure; it is suggested that the high pulmonary resistance in these patients dates from birth and is due to failure of the foetal pulmonary arteries to undergo the normal involution. The lack of response to acetylcholine may be due to paradoxical behaviour of the persisting muscular arteries (as has been demonstrated in newborn infants), or to superimposed organic intimal changes in the established cases of the syndrome investigated [see Abstract 554]. [No cases of thrombo-embolic obstructive pulmonary hypertension were included.]
S. G. Owen

SYSTEMIC CIRCULATORY DISORDERS

568. **Mechanism of Acute Hypotension from Fear or Nausea**
E. P. SHARPEY-SCHAFER, C. J. HAYTER, and E. D. BARLOW. *British Medical Journal* [*Brit. med. J.*] **2**, 878–880, Oct. 11, 1958. 4 figs., 10 refs.

Emotion, particularly fear, and nausea may cause syncope. The emotional stress of dental patients and the nausea of alcoholics treated with apomorphine were studied at St. Thomas's Hospital, London, continuous circulatory measurements being recorded immediately before and during nitrous oxide anaesthesia and apomorphine administration. Intravascular and intrathoracic pressures were measured with capacitance manometers, and changes in arterial oxygen saturation recorded by a photoelectric cell on the ear. Forearm blood flow was measured by plethysmography where possible.

Of 21 dental patients, 5 developed hypotension, with vasodilatation of the forearm vessels, tachycardia, and increased pulse pressure. In 4 of these hypotension preceded administration of the anaesthetic. In 2 cases the blood pressure, which was previously low, rose after administration of gas was started. It is suggested that fear was the main cause of the hypotension. In 5 alcoholic patients apomorphine-induced nausea caused a fall in the effective filling pressure of the heart, followed by hypotension and syncope. It is suggested that when cardiac filling pressure falls a reflex is set up. Receptors in ventricular muscle are stimulated when the ventricles are relatively empty. Impulses pass to the central nervous system and then via vasomotor nerves to cause vasodilatation in the muscles. *D. Goldman*

569. **The Carotid Sinus Syndrome.** [Review Article]
S. SALOMON. *American Journal of Cardiology* [*Amer. J. Cardiol.*] **2**, 342–350, Sept., 1958. 2 figs., bibliography.

570. **Aetiological Factors in Primary Raynaud's Disease**
J. H. PEACOCK. *British Medical Journal* [*Brit. med. J.*] **2**, 825–826, Oct. 4, 1958. 5 refs.

The author has studied the clinical history in a group of 42 patients with primary Raynaud's disease seen at the Royal Infirmary, Bristol. Clinical examination failed to reveal a local cause for the symptoms or any associated systemic disease. In 8 patients symptoms arose within 6 months of the birth of a child. In 6 others digital symptoms were related to the menopause, developing, in 4 of them, a few months after subtotal hysterectomy for fibroids. Symptoms of Raynaud's disease appeared after a period of prolonged mental stress in 7 further patients. These aetiological factors and the part played by heredity in primary Raynaud's disease are discussed. *I. McLean Baird*

Clinical Haematology

571. **Salicylate Anaemia**
W. H. J. Summerskill and A. S. Alvarez. *Lancet* [*Lancet*] **2**, 925–928, Nov. 1, 1958. 4 figs., 10 refs.

The possible role of salicylate in the causation of iron-deficiency anaemia was investigated in 2 severe cases of the condition seen at the Central Middlesex Hospital, London, in a man aged 47 and a woman aged 40. No cause for chronic anaemia had been found despite previous investigations at the hospital. Both patients had received iron therapy, intravenous and oral, at various times, in the course of 5 years and 10 years respectively, but on each occasion a good haematological response had soon been followed by haematological relapse. Repeated examination of the stools for occult blood had given only negative results. Total hysterectomy had failed to influence the anaemia in the woman; laparotomy had been contemplated in both cases.

Both patients were habitually heavy consumers of salicylate tablets for headache, and inquiry showed that this consumption had coincided with the onset and subsequent course of the anaemia in both cases. When aspirin in a dosage of 10 grains (0·7 g.) 3 times daily or soluble aspirin in a dosage of 10 grains (0·7 g.) 2 to 4 times daily was administered during a controlled period occult blood was found in the stools within 1 to 3 days; none was present before or after salicylate medication. This test is relatively non-specific, but the findings were supported by a prolonged absence of haematological relapse in both cases after the cessation of iron and salicylate consumption, the follow-up periods being 13 months and 10 months respectively. It is suggested that the habitual consumption of salicylate should be considered as a possible cause of the anaemia in similar cases.

Joseph Parness

572. **The Prophylaxis of Iron-deficiency Anaemia in Pregnancy**
D. N. S. Kerr and S. Davidson. *Lancet* [*Lancet*] **2**, 483–488, Sept. 6, 1958. 35 refs.

As a preliminary investigation before deciding upon a policy for the prophylaxis of iron-deficiency anaemia in pregnancy the authors studied the case-notes of all patients attending the antenatal clinic of the Simpson Memorial Maternity Pavilion, Edinburgh, in the months of February and March and August and September in 1955 and 1956. Patients who had any disease likely to cause anaemia or who were already receiving iron were excluded, leaving 1,994 cases for analysis. Of 1,071 women seen in the first 11 weeks of pregnancy, the haemoglobin level was below 85% (100% being taken as 14·8 g. per 100 ml.) in 32% and below 70% in 2%. But for 224 women first seen after the 24th week of pregnancy the corresponding figures were 78% and 14%. Whereas a number of other workers have reported that the incidence of anaemia in pregnancy is higher in winter than in summer, the mean haemoglobin level in the women in this series who were first seen in August and September was significantly lower than in those first seen in February and March, a seasonal variation for which no explanation could be found and which did not appear to be attributable to dietary factors In contrast to previous findings the mean haemoglobin level showed no fall with increasing age, parity, or number of pregnancies during the previous 5 years. This marked improvement probably reflects the improved economic status of the hospital population, wider recognition of the importance of menstruation and pregnancy in the aetiology of iron-deficiency anaemia, and better standards of antenatal care in recent years.

A comparative trial of oral iron therapy was then carried out on all women attending the clinic between March, 1956, and June, 1957, who were 24 weeks pregnant and whose haemoglobin level was 70% or more. The 430 women were divided at random into four groups, all of them being given pills of identical appearance to be taken 3 times a day. Group A (20%) received ferrous sulphate, Group B (20%) ferrous gluconate, Group C (20%) ferrous gluconate plus ascorbic acid, and Group D (40%) control pills containing lactose. The iron pills each contained 35 mg. of elemental iron. Samples of venous blood were taken at the start of the trial and again at the 37th week. Although 23 to 24% of the patients failed to respond to iron, the mean haemoglobin level and packed cell volume rose in each of the treated groups, whereas they fell in Group D. The mean erythrocyte count rose slightly in Group D, but the rise in each of the other groups was significantly greater. There was no significant difference in the haematological changes between Groups B and C, and it was concluded that the addition of ascorbic acid to ferrous gluconate had no potentiating effect. The increases in erythrocyte count, haemoglobin level, and packed cell volume in Groups B and C were slightly greater than in Group A, but the difference was statistically significant only in the case of the erythrocyte count. Assessment of the average dietary intake of iron in Group D showed this to be slightly below the recommended minimum of 15 mg. daily, but no close correlation could be demonstrated between a low iron intake and the incidence of anaemia. No difference was found between the four groups in the incidence of "toxic" gastro-intestinal symptoms, which was very similar to that found by the authors in a separate investigation on 93 non-pregnant women [see Abstract 490].

The authors discuss their results in relation to the prophylaxis of anaemia in pregnancy. They recommend that iron should be given in a dose of 105 mg. of elemental iron daily from the first visit to patients with a haemoglobin level below 85% and to all patients from the 24th week onwards. The slightly better response to ferrous gluconate than to the sulphate is offset by the greater cost of the former drug. Gastro-intestinal

symptoms will probably be minimized if the tablets are taken with meals and the patient assured that they will not cause discomfort. *R. F. Jennison*

573. **Studies on the *in vivo* Survival of Glycerolized and Frozen Human Red Blood Cells**
J. L. TULLIS, M. M. KETCHEL, H. M. PYLE, R. B. PENNELL, J. G. GIBSON, R. J. TINCH, and S. G. DRISCOLL. *Journal of the American Medical Association* [*J. Amer. med. Ass.*] **168**, 399–404, Sept. 27, 1958. 1 fig., 18 refs.

It has been demonstrated that human erythrocytes can withstand storage for long periods at temperatures of −80° C. or lower if they are first exposed to glycerol. This protective effect of glycerol is due to at least three factors: (1) the ice crystals formed in the presence of glycerol are small, uniform, and less disruptive on thawing than the large, irregular crystals formed in ordinary crystalloid solutions; (2) the presence of liquid glycerol prevents the high salt concentration which occurs when the water of the cells changes to pure ice; and (3) at −80° C. the glycerol becomes so viscid that it forms a mechanical barrier to the slow diffusion of cell substances. Before such erythrocytes can be used for transfusion, however, it is necessary to remove the glycerol from them, and the technical difficulties involved in this process have hitherto prevented the practical application of glycerolization in blood banks. These difficulties have been largely overcome by the use of a semi-automatic closed system of fractional centrifugation which is described elsewhere [see Abstract 574]. In the present paper from the New England Deaconess Hospital (Harvard Medical School), Boston, the authors report the transfusion into human recipients of erythrocytes stored for various periods in the frozen state after equilibration with glycerol and subsequently "deglycerolized" by this technique, and give the results of studies of the survival of such erythrocytes *in vivo*.

Altogether, the erythrocytes from 94 500-ml. units of fresh blood were glycerolized, stored at −80° or −120° C. for periods up to 19 months, deglycerolized, resuspended in the original plasma or other solution, and transfused into patients, one of whom received as many as 5 transfusions. No adverse reactions whatsoever occurred, although several patients had had febrile reactions to previous transfusions of ordinary banked blood or suffered such reactions subsequently. It is suggested that the absence of reactions may be attributable to the removal of all plasma components, leucocytes, and platelets before glycerolization and storage of the erythrocytes. After transfusion the free haemoglobin content of the plasma rose by an average of 30 mg. per 100 ml., returning to the pretransfusion level within 24 hours.

Survival studies using erythrocytes labelled with radioactive chromium (^{51}Cr) were carried out on 21 units of blood stored at −80° C. for up to 19 months and 7 units stored at −120° C. for up to 10 months. The mean immediate survival rate was 84·6%. Long-term survival studies were carried out on 4 patients, in 2 of whom the rate of disappearance of the cells was normal (50% in 30 days), while in the other 2 it was accelerated 1·4 and 2 times respectively. Both these last 2 were seriously ill; one received x-ray treatment during the month of observation, and the other had carcinoma of the intestine and the possibility of gastro-intestinal blood loss could not be excluded. *F. Hillman*

574. **Use of Biomechanical Equipment for the Long-term Preservation of Erythrocytes**
M. M. KETCHEL, J. L. TULLIS, R. J. TINCH, S. G. DRISCOLL, and D. M. SURGENOR. *Journal of the American Medical Association* [*J. Amer. med. Ass.*] **168**, 404–408, Sept. 27, 1958. 2 figs., 10 refs.

A semi-automatic, closed-system technique for the preservation of human erythrocytes with glycerol during prolonged storage at low temperatures and for the removal of the glycerol before their use for transfusion is described in this paper from the Protein Foundation and Harvard Medical School, Boston.

The central piece of apparatus used is the Cohn ADL fractionator (Tullis *et al.*, *Science*, 1956, **124**, 792), which contains two refrigerated, continuous-feed centrifuge bowls. Each bowl has an entry port which permits the successive introduction, without manual interference, of glycerolizing or deglycerolizing solutions and an outlet for the removal of plasma and waste solutions. The maximum time necessary for the glycerolization of the erythrocytes from 2 500-ml. units of blood is 50 minutes and for the reverse process 120 minutes; by increasing the number of units handled the working time per unit is reduced. The separated plasma and the glycerolized erythrocytes are collected in plastic bags, and tests for bacterial contamination are carried out at different stages of the process on samples obtained from specially provided diverticula which are separated from the containers by means of a dielectric sealer.

Details concerning the sterilization of the apparatus before use and the composition of the various solutions used in glycerolization are given, the cells being exposed to a final concentration of glycerol of 50% (w/v). After glycerolization at 5,000 r.p.m. the cells are stored at −80° or −120° C. in cabinets equipped with a warning device against rise of temperature. Before use the cells are thawed at 37° C. for about 15 minutes and the glycerol removed by automatic washing in the fractionator with solutions containing diminishing concentrations of glycerol and sufficient lactate to prevent the imbibition of water during the slow diffusion of glycerol out of the cells. After a final washing in isotonic saline the cells are resuspended in a protein-containing solution or in the original plasma for transfusion. The methods used for the determination of final glycerol content and the measurement of cell lysis are described.

Out of a total of 175 units of blood so treated, 2 showed bacterial contamination due to breaks in the plastic containers, which are brittle at very low temperatures. The maximum loss of erythrocytes was estimated at 1·8% during equilibration with glycerol and 12% during freezing, removal of glycerol, and thawing, while a further 10% loss was accounted for by the residues in the various containers and the samples taken for sterility testing. The final glycerol content of 8 units of cells tested was less than 1 g. per 100 ml. *F. Hillman*

Respiratory System

575. **Prescalene Lymph Node Biopsies. A Report of 142 Cases**
D. B. ROCHLIN and H. T. ENTERLINE. *American Journal of Surgery* [*Amer. J. Surg.*] **96**, 372–378, Sept., 1958. 16 refs.

An attempt was made to assess the value of prescalene lymph-node biopsy in the diagnosis of intrathoracic disease by analysis of the case histories of, and the biopsy findings in, 142 patients at the Hospital of the University of Pennsylvania, Philadelphia. A correlation was found between the biopsy findings and the primary pulmonary disease in 52·5% of the cases in which pathological changes could be expected from the nature of the disease. The biopsy findings were positive in 22 out of 54 patients with bronchial carcinoma and in 27 out of 34 with Boeck's sarcoid (including 15 with hilar or mediastinal lymphadenopathy). Tuberculosis, metastatic growths in the lung, carcinoma of the oesophagus, and intrathoracic lymphoma were also diagnosed in a small number of cases by prescalene lymph-node biopsy.

Complications such as section of the thoracic or right lymph duct or of the cervical sympathetic or phrenic nerve occurred in 2·6% of 155 biopsies. *I. Ansell*

576. **The Diagnostic Value of Biopsy of Nonpalpable Scalene Lymph Nodes in Chest Diseases**
T. W. SHIELDS, W. M. LEES, and R. T. FOX. *Annals of Surgery* [*Ann. Surg.*] **148**, 184–188, Aug., 1958. 9 refs.

In this paper from the Veterans Administration Research Hospital and the Municipal Tuberculosis Sanitarium, Chicago, a study is reported of the diagnostic value in chest diseases of biopsy of non-palpable scalene lymph nodes, the records of 126 patients subjected to this procedure being examined. Biopsy was carried out according to the technique of Daniels (*Dis. Chest.*, 1949, **16**, 360), care being taken during dissection to remove the fat pad lying on the anterior aspect of the scalenus anterior muscle as well as the fibro-fatty tissue under the internal jugular vein medial to the muscle. On examination of the tissue a definitive histological or bacteriological diagnosis was established in 27 (21·4%) of the cases. The biopsy findings were diagnostic in 80% of cases of Boeck's sarcoid, 20% of those of diffuse lung disease, 12·1% of cases of unilateral pulmonary disease or mediastinal lesions, and 12·1% of cases of proved lung carcinoma. The side chosen for biopsy depended on the lymph drainage of the lesion. *I. Ansell*

577. **Long-term Prophylactic Administration of Tetracycline to Chronic Bronchitics**
J. BUCHANAN, W. W. BUCHANAN, A. G. MELROSE, J. B. MCGUINESS, and A. U. PRICE. *Lancet* [*Lancet*] **2**, 719–722, Oct. 4, 1958. 28 refs.

In this trial of the value of tetracycline in chronic bronchitis, reported from the Southern General Hospital, Glasgow, two groups of 26 and 25 male patients with chronic bronchitis were compared, one group receiving 250 mg. of tetracycline night and morning, while the other (control) group received similar capsules containing lactose; all 51 patients received in addition 1 g. of yeast daily. No patient with active tuberculosis was included and none had recently received antibiotic therapy; 21 of the patients in the treatment group and 15 in the control group completed the full trial period of 12 months. Samples of each patient's sputum were first shaken with sterile glass beads, then cultured on horse-blood agar, on Fildes's peptic digest of blood agar, and on Fildes plates screened with penicillin and streaked with a penicillin-resistant staphylococcus. Serum levels of tetracycline were estimated on blood withdrawn 2 hours after the morning dose of the antibiotic, the standard used being broth containing 0·2 mg. of tetracycline per ml. and the test organism *Bacillus cereus*. An exacerbation was defined as a relapse of the bronchitic state necessitating the patient's remaining in bed for at least 5 days.

The trial showed that there was a significantly decreased number of exacerbations in the treated group, while complications of therapy, such as diarrhoea, were of a minor nature. There was no objective change in either group radiologically or physiologically, but treatment with tetracycline produced clinical improvement and reduction in the amount of cough and in the volume and pus content of the sputum. Bacteriologically, *Haemophilus influenzae* predominated in the sputum of both groups. Other organisms present were pneumococci, Friedländer's bacillus, and *Staphylococcus pyogenes*. Coliform organisms grew profusely in sputum cultures from both groups, though more often from the treated group, but yeasts were infrequent. In the treated patients who produced mucopurulent sputum pneumococci disappeared, while tetracycline-sensitive *H. influenzae* persisted. At the end of the trial tetracycline-resistant *Staph. pyogenes* was recovered from the anterior nares in 3 out of 21 treated cases. *L. Capper*

578. **Growth Conditions of Hamartoma of the Lung. A Study Based on 22 Cases Operated on after Radiographic Observation for from One to 18 Years**
K. G. JENSEN and T. SCHIØDT. *Thorax* [*Thorax*] **13**, 233–237, Sept., 1958. 2 figs., 16 refs.

From Øresundshospitalet, Copenhagen, a study is reported of the changes in size of hamartomata of the lung in 22 cases observed radiologically over a period of 1 to 18 years. In 9 cases observed for 3 or more years " unquestionable growth " was demonstrated, and in one case the size of the shadow had increased to five times the size of the shadow seen in the earliest radiograph. In 2 cases observed for 1 to 2 years no increase in growth was noted.

The age and sex distribution of the patients showed a preponderance of men in the oldest age group and of women in the younger age groups. *R. L. Hurt*

Otorhinolaryngology

579. **Pressures of the Labyrinthine Fluids.**
F. L. WEILLE, J. W. IRWIN, G. JAKO, L. L. HOLSCHUH, A. S. WEILLE, C. A. STANLEY, and M. B. RAPPAPORT. *Annals of Otology, Rhinology and Laryngology* [*Ann. Otol.* (*St. Louis*)] **67**, 858–868, Sept., 1958. 3 figs., 12 refs.

A knowledge of the pressures of the perilymph and endolymph in the living animal is of great importance for the elucidation of the process of circulation of the labyrinthine fluids. Szasz, in 1926, attempted to measure the pressure of the perilymph in dogs by means of a capillary tube passed through the membrane of the round window; but although he demonstrated that the perilymph pressure rose with that of the cerebrospinal fluid, his method did not allow accurate measurements to be made.

The present authors, working at the Massachusetts Eye and Ear Infirmary, Boston, have recorded the pressures of both perilymph and endolymph in living guinea-pigs by means of the electromanometer. A microcannula was inserted through a fenestra 30 to 40 μ in diameter in the area of the stria vascularis in the second or third turn of the cochlea for measurement of the pressure of the endolymph and through a similar fenestra just above or below this area, or through the round window, for measurement of the pressure of the perilymph, all operations being performed under a binocular dissecting microscope. Satisfactory records of endolymph pressure were made in 252 animals and of perilymph pressure in 72 (21 through the round window). The results obtained indicate that in guinea-pigs the pressure of the perilymph is higher than that of the endolymph. If this is the case Reissner's membrane, which is only 2 cells thick, must be under constant tension. From the strict biological viewpoint this would seem to be unlikely, but the difference in pressure was found in every animal examined, even though the approach to the perilymph varied, and disappeared when the animal died, so that it could hardly be a technical artefact. Moreover, differences in the biochemical composition of the endolymph and perilymph suggest that the flow of fluid is from the perilymph through Reissner's membrane to the endolymph, with the stria vascularis acting as a selective absorbing site, a hypothesis which is supported by the authors' findings. *William McKenzie*

580. **The Differential Diagnosis of Vertigo**
H. L. WILLIAMS and K. B. CORBIN. *Annals of Otology, Rhinology and Laryngology* [*Ann. Otol.* (*St. Louis*)] **67**, 869–888, Sept., 1958. 48 refs.

Ménière's disease is the most important condition to be considered in the differential diagnosis of vertigo. Its diagnosis depends on the integration of the clinical history with the results of tests of labyrinthine function and cannot be made on the basis of either of these alone. At the Mayo Clinic during 1954 632 patients [out of an unspecified total] gave vertigo or dizziness as a major complaint. About one-sixth of these patients (111) were considered to have true Ménière's disease, 131 had episodic vertigo due to circulatory disorders, 94 had vertigo on movement of the head or body, and in 32 the vertigo was dependent on the position of the head. In only 3 cases were the authors able to make a diagnosis of vestibular neuronitis. They consider the differential caloric test of Hallpike and Cawthorne to be unsuitable for clinical use because of the difficulty of establishing the end-point of the nystagmus. *William McKenzie*

581. **Anatomical Structure of the Stapes and the Relation of the Stapedial Footplate to Vital Parts of the Otic Labyrinth**
B. J. ANSON and T. H. BAST. *Annals of Otology, Rhinology and Laryngology* [*Ann. Otol.* (*St. Louis*)] **67**, 389–399, June [received Sept.], 1958. 6 figs.

The stapes is cartilaginous in the foetus of 9 weeks, but its ossification is completed during embryonic life and at birth it has the structural features which are retained almost unaltered in the adult. The authors describe the structure of the ossicle and its relations in detail. They emphasize that the footplate of the stapes is everywhere very thin, its thickness varying from 0·5 mm. to 0·04 mm. At the anterior part of the oval window penetration of 1 mm. would reach the sacculus and penetration of 2 mm. would reach the internal meatus, while at the upper margin of the footplate an upward thrust of 0·5 mm. would reach the point of entry of the utricular nerve into the macula of the utricle. The pertinence of these facts to the operation of mobilization of the stapes is underlined. *William McKenzie*

582. **Repair and Consequences of Surgical Trauma to the Ossicles and Oval Window of Experimental Animals**
R. J. BELLUCCI and D. WOLFF. *Annals of Otology, Rhinology and Laryngology* [*Ann. Otol.* (*St. Louis*)] **67**, 400–429, June [received Sept.], 1958. 13 figs., 18 refs.

It has long been maintained in the European literature that a fracture of the stapes does not heal. In experiments carried out by the authors on the monkey and the cat, however, this was not confirmed. When the stapes was removed and replaced ankylosis occurred where the footplate and vestibule touched. With a few exceptions fractures of the crura and footplate healed by new bone formation, while if bone was displaced into the labyrinth it formed callus. Depression of the stapes into the vestibule caused damage to the inner ear when the membranous labyrinth was traumatized; otherwise the end-organs showed a remarkable resistance to manipulation of the footplate and oval window.

William McKenzie

Urogenital System

583. **Treatment of Urinary Infections with Nitrofurantoin (Furadantin)**
M. SALVARIS. *British Journal of Urology* [*Brit. J. Urol.*] **30**, 303–309, Sept., 1958. 7 figs., 11 refs.

Comparative sensitivity tests carried out at St. Peter's, St. Paul's, and St. Philip's Hospitals, London, during the past 2 years have shown that nitrofurantoin (" furadantin ") is more effective *in vitro* against the common pathogenic bacteria of the urinary tract, including *Proteus vulgaris*, than any antibiotic tested with the exception of chloramphenicol. On oral administration the concentration of the drug in the urine reaches antibacterial levels within 30 minutes, while its concentration in the blood remains low (0·2 mg. per 100 ml.). The drug is safe and well tolerated.

Its clinical efficacy was tested in 145 cases of infection of the urinary tract (65 acute, 80 chronic). Of the acute cases, 45 were cured (symptom-free, urine sterile); most of the others improved, but 3 cases of *Proteus* infection were persistent. Of the chronic cases, 39 improved symptomatically (though only in 4 did the urine become sterile), while 35 were refractory to treatment.

Charles Nicholas

584. **Use of " Nilevar " (17-Ethyl-19-nortestosterone) to Suppress Protein Catabolism in Acute Renal Failure**
B. H. MCCRACKEN and F. M. PARSONS. *Lancet* [*Lancet*] **2**, 885–886, Oct. 25, 1958.

The aim of treatment in acute renal failure is to prolong life until renal function is restored, the intake of electrolytes and excessive water being avoided and, so far as possible, the catabolism of extrinsic and intrinsic protein prevented. Death in uraemia results from an accumulation of breakdown products, mainly of protein —potassium, fixed acids, urea, and other nitrogenous compounds; even with the standard glucose–water regimen a considerable amount of protein is broken down. Testosterone has been used to prevent this catabolism, and in this paper from the University and the General Infirmary at Leeds a trial is reported of " nilevar " (norethandrolone; 17-ethyl-19-nortestosterone) on 6 patients with acute renal failure following obstetric complications, 5 patients with acute renal failure from other causes, and 5 healthy medical students. The patients were given 100 g. of glucose daily with a strictly limited water intake. One healthy subject received this regimen, while the remaining 4 took a diet containing 600 Calories and providing only 2·0 g. of nitrogen and 120 g. of carbohydrate. Protein breakdown was assessed from the daily urea production. The urinary excretion of urea was measured and the daily urea accumulation in the body fluids was estimated by using an approximate figure for total body water based on the patient's weight. A control period of 4 days was followed by administration of 80 mg. of nilevar daily by mouth for 5 days.

In the obstetric patients the average reduction in protein catabolism was 70%, but in the patients with renal failure from other causes and in the medical students the decrease in protein breakdown was slight and inconstant.

David Phear

585. **Prolonged Intermittent Steroid Therapy for Nephrosis in Children and Adults**
K. LANGE, E. WASSERMAN, and L. B. SLOBODY. *Journal of the American Medical Association* [*J. Amer. med. Ass.*] **168**, 377–381, Sept. 27, 1958. 2 figs., 12 refs.

The results of prolonged intermittent steroid therapy in nephrosis are described in this paper from New York Medical College–Metropolitan Medical Center. All the patients (35 children and 11 adults) had massive oedema, marked proteinuria, hypoproteinaemia, and hyperlipaemia, due either to " lipoid nephrosis " or to glomerulonephritis. The oedema cleared completely after one or more courses of aqueous ACTH (corticotrophin), the dosage being 100 to 200 units daily for 12 to 21 days. Cortisone was then given by mouth in a dosage of 300 to 400 mg. on 3 days each week. This was continued for at least one year, and thereafter the drug was gradually withdrawn by increasing the intervals between the doses. Penicillin was given intramuscularly until diuresis was achieved, and by mouth during the period of maintenance therapy. In all patients the intake of salt was restricted.

The mortality in these 46 patients was compared with that in a control series of 185 patients observed between 1946 and 1951 who had had steroid therapy in the acute phase only or no steroid therapy at all. Had the death rate observed in the latter series applied to the former series the expected number of deaths during a 65-month period would have been 13; actually, only one of the 46 patients died over a period of 65 months. The blood chemistry became normal in all except 2 patients; 25 had no residual proteinuria, while a further 19 had only a trace. Recurrence of oedema after infections responded to a full course of steroid therapy. [The recurrence rate is not discussed.]

There were no serious side-effects. The children grew and developed normally, which is not always the case in those receiving prolonged intermittent steroid treatment.

T. B. Begg

586. **Richard Bright and His Discovery of the Disease Bearing His Name**
W. HALE-WHITE. *Guy's Hospital Reports* [*Guy's Hosp. Rep.*] **107**, 294–307, 1958. 1 ref.

587. **Bright's Disease. The Changing Concept of a Century**
W. N. MANN. *Guy's Hospital Reports* [*Guy's Hosp. Rep.*] **107**, 323–347, 1958. Bibliography.

Endocrinology

588. **Recurrent Renal Calculi and Hyperparathyroidism**
H. W. McIntosh, J. A. Balfour, and M. H. Duffy. *British Journal of Urology* [*Brit. J. Urol.*] **30**, 292–296, Sept., 1958. 4 figs., 2 refs.

As a result of the investigation of a group of 50 patients, all males, with recurrent renal calculi at Shaughnessy Hospital, Vancouver, for evidence of hyperparathyroidism, 5 cases of operatively proved primary hyperparathyroidism were detected. Determination of the serum calcium level was not always helpful. The most reliable combination of tests was measurement of the urinary excretion of calcium while the patient received a standard low-calcium diet with the simultaneous estimation of the tubular reabsorption of phosphate. All 5 patients with hyperparathyroidism showed a high urinary calcium concentration and low tubular reabsorption of phosphate. *G. W. Csonka*

THYROID GLAND

589. **Use of Triiodothyronine for Reduction of Goiter and Detection of Thyroid Cancer**
P. Starr and W. Goodwin. *Metabolism* [*Metabolism*] 7, 287–292, July, 1958. 4 figs., 11 refs.

At Los Angeles County Hospital triiodothyronine was tried in treatment of 36 patients with palpable goitre, the non-toxicity of which was judged clinically and from the uptake of radioactive iodine by the thyroid and the serum protein-bound iodine (PBI) level. The drug was given in an initial dosage of 25 μg. twice daily, increasing every few weeks if the PBI level was not reduced. Thyrotoxicosis factitia usually occurred when the dosage reached 200 to 300 μg. a day, but in one case up to 400 μg. a day was given with benefit. In all cases there was a reduction in the size of the goitre as judged by palpation, and in more than half the cases the estimated weight of the gland fell below 50 g. In one patient in whom a portion of the gland did not diminish in size while the remainder became impalpable operation revealed that the persistent portion of the gland was an encapsulated follicular adenocarcinoma. However, in several other cases in which operation was carried out because a nodule failed to regress only benign tissue was found. *D. G. Adamson*

590. **Effect of Thyroxine, Triiodothyronine and Triac on Metabolic Rate, Blood Lipids and Thyroid Size and Function in Subjects with Non-toxic Goitre**
D. Doniach, R. V. Hudson, W. R. Trotter, and A. Waddams. *Clinical Science* [*Clin. Sci.*] **17**, 519–529, 1958. 7 figs., 13 refs.

This paper from the Middlesex Hospital and University College Hospital Medical Schools, London, reports a study of the effects of triiodothyronine, its acetic acid analogue triiodothyroacetic acid (triac), and thyroxine on the basal metabolic rate (B.M.R.), the blood lipid level, and the size and function of the thyroid gland in 50 euthyroid women with non-toxic goitre, which in 14 cases was judged to be diffuse and in 36 nodular. In no case were antibodies against a thyroid extract demonstrated in the serum. The 3 drugs and lactose, which was used as a control, were prepared in indistinguishable tablets, the patients divided at random into 4 groups, and each group then treated for 3 months with one type of tablet, the nature of which was unknown to patient or observers. Thyroxine was given in a daily dosage of 0·2 mg. for the first 4-week period, 0·3 mg. for the second 4 weeks, and 0·4 mg. for the last period. The corresponding doses of triiodothyronine were 0·04, 0·06, and 0·08 mg. respectively, and of triac 2, 3, and 4 mg. in the 3 periods respectively. The B.M.R. was calculated from measurement of oxygen consumption, the serum total cholesterol and α- and β-lipoprotein levels were estimated separately by methods described, the latter being separated by paper electrophoresis, the uptake of radioactive iodine was measured by external counting 24 hours after administration of a tracer dose, while the size of the thyroid gland was estimated by palpation by the same observer, who was ignorant of the treatment received. The 4 groups were comparable in all important respects at the start of treatment. As 3 patients had to be withdrawn because they developed severe symptoms of hyperthyroidism while taking thyroxine, and one was excluded for irregular attendance and 2 because they became pregnant, only 44 patients completed the trial.

Symptoms of hyperthyroidism were noted in 3 patients receiving triac and in 6 receiving thyroxine so that, including the 3 cases mentioned above, 9 out of 12 patients given thyroxine developed symptoms of hyperthyroidism. The B.M.R. and the mean pulse rate rose only in the thyroxine- and triac-treated groups. The mean body weight and uptake of radioactive iodine fell in all 3 treated groups, and both values rebounded after treatment had ceased. The control (lactose) group showed no change in these respects, but did show a rise in the mean serum cholesterol level, whereas this level fell by approximately 20% in all 3 hormone-treated groups, as did also the total lipoprotein level, which however remained unchanged in the lactose group. The α-lipoprotein level showed no significant change during treatment in any group, but rose in the thyroxine and triiodothyronine groups after the end of treatment. The β-lipoprotein level remained unchanged in the lactose group, but fell by a maximum of 30% in all the treated groups, with a tendency to rebound at the end of treatment. A reduction in the size of the goitre was recorded in 2 out of the 13 cases in the lactose group and in 15 of 34 cases in the treated groups, being greatest in the triac group (8 cases out of 13 cases). Thus in the doses used in this trial thyroxine had the greatest effect in terms of symptoms, pulse rate,

weight loss, and elevation of the B.M.R., while all 3 drugs had a comparable lowering effect on the serum lipid level. In regard to thyroid size the authors draw no firm conclusions because of the small number of patients involved, but triac seemed to have some advantages which might be worth confirming by a larger trial.

Charles Rolland

591. **The Biological Effect of Radioactive Iodine Administered by Different Routes.** (Биологическое действие радиоактивного йода при различных методах его введения)

A. A. Атавек. *Проблемы Эндокринологии и Гормонотерапии* [*Probl. Endokr. Gormonoter.*] **4**, 13–20, No. 4, July–Aug., 1958. 7 figs., 4 refs.

The author has studied the differences in effect, if any, of administering radioactive iodine (^{131}I) to young rats in a single dose and in divided dosage. For this purpose the animals were divided into 11 groups (8 rats in each) 5 of which were given subcutaneously 200, 300, 400, 500, or 800 μc. of ^{131}I in a single dose, while the other 5 groups received the same total doses but administered in 6 weekly injections; the 11th group which received no ^{131}I served as a control. The animals were weighed at intervals of 10 days. At the end of 7 weeks the control group of rats had gained an average weight of 148 g., the animals receiving 800 μc. in a single dose had gained only 33 g., while those receiving 800 μc. in 6 weekly injections had gained 94 g. The arrest of growth in the groups given the smaller doses was less pronounced, but in all cases was greater in those receiving single doses than in those given the same dose in fractions, as also was the degree of histological change seen in the thyroid glandular tissue.

It is therefore concluded that in controlling the function of the thyroid gland in thyrotoxicosis by means of fractional dosage of ^{131}I it is necessary to increase the quantity of the isotope which would be given in a single dose by a factor of 1·5 to 2. *L. Firman-Edwards*

592. **The Thyroidal Accumulation as a Clinical Test for Hyperthyroidism**

I. J. L. Goldberg and E. A. Fitzsimons. *British Journal of Radiology* [*Brit. J. Radiol.*] **31**, 428–432, Aug., 1958. 2 figs., 21 refs.

At the West London Hospital the authors have compared the efficiency of 8 different tests of thyroid function based on the uptake of radioactive iodine (^{131}I) by the thyroid gland. The tests were (1) the thigh:neck clearance ratio described by Foote and Maclagan, (2) Berson's clearance test, (3) the neck:thigh ratio at 2 hours as proposed by Myant and Pochin, (4) the 2-hour uptake of ^{131}I, (5) the 24-hour uptake of ^{131}I, (6) the urinary excretion "T" index test of Fraser *et al.*, (7) the 8-to-24-hour excretion fraction test of Arnott *et al.*, and (8) the thyroid ^{131}I-clearance test which, for reasons which are outlined, was adopted as standard for comparison. This last test, however, is more complex to perform and, although probably the most accurate, causes the patient more inconvenience than simpler tests. The estimations were carried out with conventional apparatus.

The coefficients of correlation between the pairs of results of the thyroid clearance test and each of the other uptake tests were determined for 100 euthyroid patients, these being selected for this purpose in order to minimize dependence on thyroid status. A correlation coefficient of between 0·6 and 0·8 was obtained on all the tests except the Berson clearance test, for which it ranged from 0·42 to 0·65. The results were further examined in order to determine the proportion of the 30 hyperthyroid patients in the series who were incorrectly diagnosed by each test. This showed that the 24-hour-uptake test compared unfavourably with the others, resulting in 12 incorrect diagnoses out of 30, as against 1 to 4 incorrect diagnoses by the other tests. Discussing the efficiency and convenience of the tests the authors conclude that the neck:thigh ratio at 2 hours and the 8-to-24-hour excretion fraction are simple and effective tests suitable for routine clinical use, the former having the added advantage that the result is known the same day. They point out that it is possible also to use ^{132}I for these tests, with consequent reduction in the amount of exposure of the gland to radiation for an equivalent dose, since this isotope has a half-life of only 2·33 hours.

I. M. Rollo

593. **A Comparison of Radioiodine Tests in the Diagnosis of Hyperthyroidism**

A. W. G. Goolden. *British Journal of Radiology* [*Brit. J. Radiol.*] **31**, 433–436, Aug., 1958. 3 figs., 16 refs.

In experiments carried out on 120 patients with thyrotoxicosis, 50 untreated and 70 previously treated with radioactive iodine (^{131}I), three methods of assessing thyroid status were compared. (1) The thyroid clearance test was performed by measuring the uptake of ^{131}I for 35 to 40 minutes with a scintillation counter, blood samples being taken 25 minutes after the intravenous administration of the tracer dose. (2) The "T" index of urinary excretion of ^{131}I was determined in three fractions during 48 hours. (3) The plasma protein-bound ^{131}I level was determined 48 hours after the tracer dose.

The most effective separation between euthyroid and hyperthyroid patients in both the treated and untreated groups was obtained by the thyroid clearance test, 95% of all cases being correctly diagnosed, assuming an upper limit of 60 ml. per minute for the normal clearance value. With the T index test the distinction between euthyroid and hyperthyroid patients was satisfactory in regard to the untreated group, but there was considerable overlapping in the treated group. The values for protein-bound ^{131}I covered a higher range in treated patients than in the untreated, and there was no effective separation between patients who had become euthyroid and those with residual hyperthyroidism. A possible disadvantage of the thyroid clearance test might be impairment of organic binding, as had previously been reported by Kirkland in patients examined 6 to 8 weeks after ^{131}I therapy, but the present author observed no such impairment in patients tested 3 or more months after such therapy. It is his opinion that, despite certain difficulties, the thyroid clearance test is the most reliable method of measuring thyroid function, while it has the additional advantages

of being completed within 35 minutes and of not depending on the cooperation of the patient. This paper contains a short [and interesting] discussion of the kinetics of iodine accumulation by the thyroid gland.

I. M. Rollo

594. **Factors Affecting the Choice of a Routine Radioactive Iodine Test for Thyroid Activity**
N. HOWARD, J. M. MCALISTER, and M. B. MCEVEDY. *British Journal of Radiology* [*Brit. J. Radiol.*] **31**, 437–438, Aug., 1958. 2 figs., 15 refs.

Writing from University College Hospital, London, the authors review the many methods in which radioactive iodine (^{131}I) is used in the assessment of thyroid activity. They conclude on the basis of the findings in 139 patients, both euthyroid and hyperthyroid, that the results obtained by the 2-hour neck:thigh ratio test are as useful as those obtained by any other simple technique. Further, this test has the great advantage that in performing it the short-lived isotope ^{132}I can be used, with a consequent decrease in the degree of exposure of the patient to radiation. They point out that a clear-cut diagnosis can be made in the majority of cases of suspected hyperthyroidism, and that in the doubtful cases a more detailed investigation can be carried out using ^{131}I.

I. M. Rollo

595. **Studies on the Effect of Thyrotropic Hormone on the Thyroid Function in Man.** [Monograph, in English] J. EINHORN. *Acta radiologica* [*Acta radiol.* (*Stockh.*)] Suppl. 160, 1–107, 1958. 23 figs., bibliography.

596. **The Free Achilles Reflex in Hypothyroidism and Hyperthyroidism**
J. D. LAWSON. *New England Journal of Medicine* [*New Engl. J. Med.*] **259**, 761–764, Oct. 16, 1958. 7 figs., 14 refs.

Slowing of the tendon reflexes has long been known as a clinical manifestation of hypothyroidism, but no suitable apparatus has hitherto been devised to give a quantitative estimate of this slowing which could be used in diagnosis. The author describes a simple method of recording the ankle reflex. With the patient in the kneeling position, a horseshoe magnet is fixed to the plantar surface of the heel with adhesive tape. When the ankle reflex is elicited the movement of the magnet induces, in a coil held nearby, a current which is fed into a direct-writing electrocardiograph.

Records of the reflex were obtained from 550 euthyroid subjects, 24 patients with hyperthyroidism, and 21 with hypothyroidism. Measurement of the interval between the stimulus and the end of the contraction phase proved to be the most reliable means of differentiating between normal and abnormal responses. This interval ranged from 140 to 240 milliseconds in the euthyroid subjects, from 108 to 156 milliseconds in the hyperthyroid subjects, and from 236 to 360 milliseconds in the hypothyroid subjects. Records from patients with other pathological states showed no significant change in the speed of the reflex. Certain drugs, however, have been shown to shorten or prolong the contraction in normal subjects.

G. S. Crockett

ADRENAL GLANDS

597. **Neuro-psychiatric Complications of Treatment with Cortisone and Corticotrophin.** (Нервно-психические изменения при лечении кортизоном и АКТГ) T. A. NEVZOROVA. *Клиническая Медицина* [*Klin. Med.* (*Mosk.*)] **39**, 17–24, No. 9, Sept., 1958. 21 refs.

Psychiatric complications occurring during treatment with cortisone and ACTH are not rare and usually appear either at the beginning or at the end of treatment. When they occur at the beginning they are mostly manifested by euphoria, which no doubt is due to the stimulating effect of the hormones, while at the end of treatment they usually take the form of psychoses (such as maniacal or depressive conditions), a sense of fear, epilepsy or status epilepticus, syndromes of disorientation, or an amnestic syndrome. A state of agitation or fear may be a prodromal symptom. The mechanism of these psychiatric symptoms at the end of the treatment is not clear, but it is possible that they may be due to metabolic changes.

For the prevention of these disturbances the following measures are suggested. (1) Corticoid treatment should always be accompanied by a strict control of potassium and calcium metabolism. (2) The diet should be poor in chlorides, plenty of vegetables and fruit being given to diminish the intake of sodium chloride. (3) The intake of preparations containing ascorbic acid and potassium ions, in particular potassium bromide and potassium citrate, must be carefully regulated. (4) The sudden withdrawal of cortisone and ACTH must be avoided at all costs.

H. W. Swann

598. **Urinary Excretion of 17-Ketosteroids in Children**
M. PROUT and A. H. SNAITH. *Archives of Disease in Childhood* [*Arch. Dis. Childh.*] **33**, 301–304, Aug., 1958. 11 refs.

The urinary 17-ketosteroid excretion of 73 normal children and of children with adrenal hyperplasia (32 cases), tumours of the adrenal cortex (7 cases), and precocious puberty (4 cases) has been studied at the Hospital for Sick Children, Great Ormond Street, London. Various methods of estimation were employed, and are described. Considerable variation was found in the values obtained by the different techniques; from a comparison of the results with one another and with those of other workers, the authors conclude that the M.R.C. method using alcoholic potassium hydroxide (*Lancet*, 1951, **2**, 585) is the most satisfactory routine procedure.

The mean output of 17-ketosteroids in children in four age groups (0–1, 1–5, 6–10, and 11–17 years) is tabulated. Figures are also given for the 17-ketosteroid excretion of children of various ages with dysfunction of the adrenal cortex, and show that adrenal hyperplasia and adrenocortical tumour cannot be distinguished from each other by this test alone; pregnanetriol output and the plasma electrolyte level must also be taken into account. The authors state that tests with ACTH are of little value in the diagnosis of congenital adrenal hyperplasia. In boys showing signs of precocious pu-

berty the 17-ketosteroid output is unlikely to exceed 10 mg. per day; if the level of excretion is over 10 mg. per day a virilizing tumour is more probable, but special investigations would be required to exclude such a tumour. *Nancy Gough*

599. **Cancer of the Adrenal Cortex. The Natural History, Prognosis and Treatment in a Study of Fifty-five Cases**
D. A. MACFARLANE. *Annals of the Royal College of Surgeons of England* [*Ann. roy. Coll. Surg. Engl.*] **23**, 155–186, Sept., 1958. 14 figs., 28 refs.

The author describes the clinical features of 55 cases of carcinoma of the adrenal cortex seen at various teaching hospitals in London. The "non-hormonal" tumours (20 cases), that is, those not producing hormones, presented as a pain or a mass in the loin or abdomen, or were recognized by the presence of metastases. Haematuria, if the kidney is invaded, intermittent low-grade pyrexia, or adrenal apoplexy may also be presenting features. In 35 of the patients the tumour presented with "hormonal" symptoms; in this type virilism is the commonest manifestation (22 cases), Cushing's syndrome being noted in only 7 cases. Estimation of urinary steroid hormone excretion is essential for diagnosis.

A modification of the "T.N.M." system of clinical staging proposed by Denoix is described, some such method of staging being valuable in assessing prognosis. By this means 42 of the tumours could be staged preoperatively, 22 being in either Stage I or II and 20 in Stage III or IV. The immediate mortality among 42 surgically treated cases was high—12 deaths, or 28·5% [elsewhere in the paper stated to be 11 (26·2%)]. But of 20 patients treated by radical excision of the tumour, 13 (10 females and 3 males) survived for 3 years. The improvement in the immediate mortality in cases treated after 1952 when cortisone was more readily available is pointed out, and the importance of ensuring adequate preoperative steroid therapy is emphasized.
I. McLean Baird

DIABETES MELLITUS

600. **Chlorpropamide. A New Hypoglycaemic Agent**
I. MURRAY, M. J. RIDDELL, and I. WANG. *Lancet* [*Lancet*] **2**, 553–554, Sept. 13, 1958. 6 refs.

Of the earlier oral hypoglycaemic agents, carbutamide has been regarded as being too toxic, while tolbutamide is less potent and has a shorter duration of action. In this paper from the Victoria Infirmary, Glasgow, the authors report the results of a trial with a new preparation, chlorpropamide (N-propyl-N-(*p*-chlorobenzene sulphonyl) urea). All the 43 patients selected for the trial, of whom 13 were in-patients and 30 out-patients, had had diabetes for less than 10 years, were over 40 years of age, had been taking insulin, if at all, for not more than 2 years, and only 2 of them were obese. The dose of chlorpropamide was 1 g. daily, taken at breakfast.

With this dosage a satisfactory response was obtained in 28 of the 43 patients treated, and this generally became evident by the second or third day, and always within 7 days. Tests of the urine for sugar usually showed no sugar or only an occasional trace, and the mean blood sugar level fell from 273·5 mg. per 100 ml. before treatment to 161·8 mg. per 100 ml. at the end of 2 weeks. Determination of the 24-hour urinary glucose output in in-patients who responded showed that the mean value fell from 35·5 g. to 3·4 g. The impression gained was that chlorpropamide is somewhat less potent than carbutamide, but definitely more potent than tolbutamide. There were no serious toxic effects and no evidence of leucopenia or thrombocytopenia. Mild side-effects in 9 cases included nausea in 7, a diffuse erythematous rash in one, and drowsiness unaccompanied by hypoglycaemia in one. Because of this evidence of potential toxicity of the drug, particularly in a few patients given higher doses, it was concluded that the dose of chlorpropamide should not exceed 1 g. daily. The authors therefore provisionally advise beginning treatment with 1 g., daily taken as a single dose, and reducing this to the lowest effective level as soon as a good response is obtained. *K. O. Black*

601. **The Mechanism of the Hypoglycaemic Action of Antidiabetic Sulphanilamide Preparations.** (К механизму гипогликемического действия антидиабетических сульфаниламидных препаратов)
S. M. LEJTES and N. P. SMIRNOV. *Проблемы Эндокринологии и Гормонотерапии* [*Probl. Endokr. Gormonoter.*] **4**, 3–12, No. 4, July–Aug., 1958. 29 refs.

The authors discuss the mode of action of the sulphonylurea compounds carbutamide and tolbutamide which lower the blood sugar level when administered by mouth. They consider that there is no definite evidence for the suggestion that these substances injure the protoplasm of the α cells of the pancreatic islets and so inhibit the formation of glucagon. Another suggestion is that they stimulate the pancreatic β cells to produce more insulin. If this were so, prolonged use of these preparations might therefore be expected to cause exhaustion and subsequent degeneration of these cells, but the authors have found no evidence of such changes. It has also been suggested that the sulphonylureas suppress the activity of phosphokinase, while other workers have postulated a lowered activity of glucose-6-phosphatase. But the theory with which the authors are most in agreement is that of Mirsky *et al.* (*Metabolism*, 1956, **5**, 156; *Abstr. Wld Med.*, 1956, **20**, 137), who showed *in vitro* and *in vivo* that these substances lower the activity of liver insulinase.

In a series of animal experiments the present authors demonstrated that carbutamide suppresses the activity of liver insulinase in both normal and diabetic animals (pancreatectomized dogs and alloxan-treated rabbits) and so increases the hypoglycaemic effect of administered insulin. Thus of 4 groups of rabbits given carbutamide and insulin in various forms, the group receiving insulin incubated with unaltered dialysed liver extract showed a fall in the blood glucose level of only 8·5%, compared with a mean of 27% in the other groups, owing to destruction of the insulin by liver insulinase.

This suggests that carbutamide destroys insulinase both *in vivo* in the liver and when added to the dialysed extract *in vitro*.

Furthermore, in fully depancreatized dogs and in rabbits with severe alloxan diabetes carbutamide exhibited no hypoglycaemic effect by itself, but in animals with mild alloxan diabetes in which some islet tissue was still present it exerted its usual hypoglycaemic action. The authors conclude that this explains why carbutamide cannot lower the blood sugar level in the absence of insulin, but can potentiate the action of insulin, whether the latter is produced by the islets or administered parenterally. *L. Firman-Edwards*

602. **The Effect of Insulin-binding Antibodies on Insulin Sensitivity**
N. KALANT, C. GOMBERG, and R. SCHUCHER. *Lancet* [*Lancet*] **2**, 614–617, Sept. 20, 1958. 4 figs., 10 refs.

In studies carried out at McGill University, Montreal, using insulin labelled with radioactive iodine (^{131}I) it was demonstrated that a group of 14 diabetic patients previously treated with insulin showed a smaller insulin response (in terms of half-life of blood glucose) than a group of 11 similar patients not previously treated with insulin. It was further shown that the insulin response was not related to the degree of globulin binding of insulin or to the degree of insulin retention in the circulation. In the previously treated patients the insulin in the serum was associated with the β-globulin fraction (although on paper electrophoresis it apparently moved with the γ globulin), whereas in the untreated patients it was diffusely associated with many serum protein fractions.

In experiments on rabbits the induction of haemagglutinating antibodies by the injection of insulin resulted in the binding of insulin to serum globulin and a decreased rate of removal of insulin from the circulation, but not to any decrease in the hypoglycaemic response to insulin or to development of anti-insulin activity. The passive immunization of 5 rabbits with serum from insulin-treated diabetics led to a variable increase in the degree of globulin binding of insulin, but did significantly slow the removal of insulin from the circulation. It is therefore concluded that the development of insulin antibodies does not appear to account for the decreased responsiveness to insulin or for its slower removal from the circulation observed in insulin-treated diabetic patients.
F. W. Chattaway

603. **Hypophysectomy in Severe Diabetes. I. Neurosurgical Aspects**
M. JAVID, E. S. GORDON, and T. C. ERICKSON. *Journal of Neurosurgery* [*J. Neurosurg.*] **15**, 504–511, Sept., 1958. 5 figs., 10 refs.

The increased expectation of life of diabetics as a result of modern methods of treatment of the disease has at the same time led to an increasing incidence of severe retinopathy and nephropathy, especially in juvenile diabetics. The authors of this paper from the University Hospitals, Madison, Wisconsin, report the results of surgical treatment of 15 patients with severe loss of vision from diabetic retinopathy and varying degrees of nephropathy, hypophysectomy having been performed on 10 and section of the pituitary stalk on 5. The patients (4 female and 11 male aged 19 to 61 years) had been known diabetics for 9 to 29 years. One patient was a pituitary dwarf and another was acromegalic. The operation was performed under general anaesthesia by a subfrontal approach on the side of the more severely affected eye. In general, operation resulted in a marked decrease in insulin requirements with a lowering of the average blood pressure. There was consistent improvement in the diabetic retinopathy with some improvement in nephropathy; in some cases vision returned. (The results of extensive metabolic and endocrine studies are to be the subject of a separate report.) Of the 15 patients, 3 died within the first 8 days following surgery and 5 died 3 to 26 months afterwards; 5 of these 8 deaths were due to prolonged hypoglycaemia.

It is concluded that section of the pituitary stalk is not equivalent to hypophysectomy, since there is great variation in the amount of destruction of the anterior lobe as a result of section. Hypophysectomy is not indicated as a routine therapeutic procedure in juvenile diabetics, but it may have a place in the management of selected patients with severe diabetes and nephropathy.
J. B. Stanton

604. **The Treatment of Diabetes Mellitus with Sulphanilamide Drugs.** (Клинический опыт применения сульфаниламидных препаратов для лечения больных сахарным диабетом)
M. V. VOGRALIK. *Клиническая Медицина* [*Klin. Med. (Mosk.)*] **36**, 87–93, No. 10, Oct., 1958. 4 figs., 33 refs.

Reporting a clinical trial of two sulphanilamide preparations, "rastinon" (tolbutamide) and "nadisan" (carbutamide), in the oral treatment of diabetic patients the author found tolbutamide to be superior to carbutamide, its greatest advantage being the almost complete absence of toxic side-effects.

It was found that tolbutamide in doses of 1·5 to 3 g. per day could completely replace insulin in the treatment of mild forms of diabetes and partially replace it in the moderately severe forms; but in a number of the latter, as well as in the graver cases, the treatment had to be supplemented with insulin. The best results were achieved in patients over 40 who were inclined to obesity. Although the mechanism of action of the drug is still uncertain, it is already clear that it affects not only carbohydrate metabolism, but also that of fat, and inhibits the development of ketosis. *A. Orley*

605. **Substances Used in Treatment of Diabetes Mellitus.** [Review Article]
E. TOLSTOI. *American Journal of the Medical Sciences* [*Amer. J. med. Sci.*] **236**, 625–633, Nov., 1958. 21 refs.

606. **Diabetes Mellitus.** [Review Article]
S. B. BEASER. *New England Journal of Medicine* [*New Engl. J. Med.*] **259**, 525–532 Sept. 11, and 573–581 Sept. 18, 1958. Bibliography.

The Rheumatic Diseases

ACUTE RHEUMATISM

607. **The Value of the Study of the Serum Perchlorate-soluble Seromucoids and Orosomucoid in the Management of Rheumatic Fever.** (Intérêt de l'étude des séromucoïdes perchlorosolubles et de l'orosomucoïde dans la surveillance du rhumatisme articulaire aigu)
G. BISERTE, A. BRETON, R. HAVEZ, and G. FONTAINE. *Archives françaises de pédiatrie* [*Arch. franç. pédiat.*] **15**, 800–815, 1958. 5 figs., 31 refs.

Among the battery of tests employed for the diagnosis of acute rheumatic fever and for following its clinical course during and after hormone treatment one of the most valuable is the study of the serum glucoprotein level, and particularly of its acid fractions, the perchlorate-soluble seromucoids. In a study here reported from the Department of Paediatrics, University of Lille, of 23 cases of acute rheumatic fever the authors found that the serum mucoid level was invariably elevated in the presence of rheumatic activity, even in the rare cases in which the erythrocyte sedimentation rate was normal (as in heart failure). This elevation could be demonstrated either by chemical analysis or by paper electrophoresis at a *p*H of 3·9; the latter method is simple and easy to perform. During treatment the level of serum mucoids is the slowest to return to normal, and in the authors' experience it is unwise to stop treatment until normal levels are reached, since otherwise relapse is liable to occur. *John Lorber*

608. **Recurrent Attacks of Acute Rheumatism in School-children**
R. A. N. HITCHENS. *Annals of the Rheumatic Diseases* [*Ann. rheum. Dis.*] **17**, 293–302, Sept., 1958. 9 refs.

An analysis is presented of recurrent attacks of acute rheumatism in Cardiff school-children during the years 1931–50, before specific prophylaxis was carried out on a wide scale, with special reference to recurrence in children who showed evidence of heart disease at some time during the observation period. Recurrence is defined as one or more major manifestations of acute rheumatism occurring after a period of not less than 3 months from the end of the previous acute attack. Some 38% of 189 boys and 32% of 291 girls had recurrent attacks, the difference in sex incidence not being significant. The risk of recurrence was low in children with "silent" carditis alone. In those in whom the disease started with chorea it was probable that a recurrence would also take the form of chorea. The percentage risk of a recurrence was 9 in the first year after onset, increasing to 15 in the second year and remaining around this figure for 3 years; it declined thereafter, but was still substantial in the seventh year after onset. Age was an important factor; there was a relatively low risk of recurrence up to the age of 7 years and a greatly increased risk from 7 to 13 years. Residual cardiac damage was noted in 77% of children who had recurrent attacks and in precisely the same percentage of those who had no recurrence. The author states that the findings do not provide "conclusive evidence of a true decline" in the frequency of recurrence over the period. Seasonally, in 36% of cases onset of the initial attack of acute rheumatism occurred in the fourth quarter of the year compared with 23% in the first quarter, but 40% of recurrences were experienced in the first quarter as against 28% in the fourth quarter. There was some indication that in children in poor social circumstances the recurrence rate tended to be higher than in children from well-to-do homes.
William Hughes

609. **Sydenham's Chorea**
M. LESSOF. *Guy's Hospital Reports* [*Guy's Hosp. Rep.*] **107**, 185–206, 1958. 7 figs., 44 refs.

The author reviews the literature and presents an analysis of 210 attacks of chorea seen during a period of 8 years at the Canadian Red Cross Memorial Hospital, Taplow, Bucks, in 175 patients, of whom 148 had single attacks, 22 had 2 attacks, 3 had 3, one 4, and one 5. In discussing sex incidence the author points out that of 1,000 patients admitted to the hospital with rheumatic fever (including 209 with chorea), 511 were female and 489 male, whereas of the 209 with chorea, 133 were girls and 76 boys. The age ranged from 3 to over 22, the maximum incidence being in the age group 6 to 14. Of 19 patients with chorea over the age of 15, only one was a male. The series included 3 cases of chorea gravidarum. Among the 36 most severe cases the sex difference was still more marked, 30 of these patients being female. The duration of the chorea varied; excluding 4 patients who died of carditis while still choreic and one who died of chorea and hyperpyrexia, about half the patients recovered in 10 weeks, many recovered in less than a week, while in others symptoms persisted for a year or more.

As regards the association of chorea with rheumatic fever, the modified Duckett Jones criteria for the diagnosis of rheumatic fever were satisfied in 117 of the cases. Arthritis was observed in 36·8% of first attacks and in 15% of subsequent attacks. Carditis occurred in 72·8% of first and in 67·1% of subsequent attacks. The corresponding figures for rheumatic nodules were 21·3 and 11·0% and for erythema marginatum 6·7 and 6·8% respectively. Two of the patients had systemic lupus erythematosus. In those with arthritis or joint pains there was usually a delay of from 4 to 24 weeks or more between the onset of joint symptoms and the development of chorea, and in only 6 out of 63 cases did chorea precede the joint symptoms. In 14 cases of rheumatic fever chorea developed after the erythrocyte sedimentation rate had returned to normal. There was no significant difference between the incidence of different types

of heart murmur in acute rheumatic fever and in chorea. Of 131 patients who had carditis with chorea, 102 had a basal aortic diastolic murmur, 95 a mitral diastolic murmur, 42 a mitral pansystolic murmur, and 10 a presystolic murmur. Less than 20% of the patients seen at a follow-up clinic had a recurrence while under observation, but out of 166 followed up, 46 continued to have chorea-like movements, usually when they were tired or excited, for an average of 11 months after the chorea had disappeared. In 2 of the fatal cases studied post mortem no clear-cut abnormalities could be demonstrated in the central nervous system. The pathology and treatment of chorea are discussed.

C. Bruce Perry

CHRONIC RHEUMATISM

610. **Hexylresorcinol (Caprokol) in the Treatment of Arthritis**

E. A. LIPKIN. *Rheumatism* [*Rheumatism*] **14**, 111–113, Oct., 1958. 4 refs.

This is a brief report of the treatment in general practice of 165 patients with rheumatoid arthritis or osteoarthritis by the daily oral administration of "caprokol", "iodolysin", ascorbic acid, and "hypon" [a compound analgesic containing aspirin, phenacetin, codeine, caffeine, and phenolphthalein]. Caprokol is an oily solution of hexylresorcinol, the dose of which ranged from 0·45 to 1·8 g. a day. Iodolysin (thiosinamine ethyl iodine), which is claimed to have a softening effect on cicatrices, was given in a dose of not more than 240 mg. a day. The dose of ascorbic acid was 300 mg. a day. Treatment with caprokol was continued for periods up to 5 years and the dosage was varied according to the needs of the individual patient, but iodolysin was given only for the first 4 months; full details are not given. Improvement was assessed from general mobility, joint circumference, mobility in extension, and grip strength, 104 patients being "much improved", "some improvement" being obtained in 50 others, and little or no improvement in 11.

[The data contained in this paper are not really sufficient for a critical assessment to be made of the value of these drugs.] *K. C. Robinson*

611. **The Clinical and Metabolic Effects of 16-alpha-Methyl-9-alpha-fluoroprednisolone ("Dexamethasone")** (Effetti clinici e metabolici del 16-alfa metil-9 alfa-fluoroprednisolone o desametasone)

L. VILLA, C. B. BALLABIO, and G. SALA. *Rheumatismo* [*Rheumatismo*] **10**, 127–133, May–June [received Sept.], 1958. 4 figs., 5 refs.

The effects of dexamethasone ("decadron") were studied at the General Medical Clinic of the University of Milan in 15 patients, of whom 10 had rheumatoid arthritis, 2 rheumatic fever, one chronic gout, one scapulo-humeral periarthritis, and one Paget's disease. In each case the previous requirement of prednisone or of triamcinolone had been carefully evaluated. Dexamethasone was given in daily amounts of 0·5 to 6·0 mg. in 3 or 4 divided doses. The clinical effects on the various disease processes were fully comparable to those achieved with the other steroids, showing that dexamethasone is 4·2 to 10 (average 7·1) times more active than prednisone and 4 to 10 (average 7) times more active than triamcinolone.

The results of laboratory studies were as follows. (1) Plasma electrolytes before, during, and after treatment were unaffected, and water retention or potassium loss was not observed. (2) Diabetogenic effects did not appear in 4 normal subjects, while in one patient with a diabetic syndrome induced by prednisone and triamcinolone the glycosuria disappeared under treatment with dexamethasone; in another patient with diabetes aggravated by prednisone, triamcinolone, and ACTH there was a distinct improvement in the diabetic state. (3) Nitrogen metabolism appeared to be slightly increased when dexamethasone was given in high dosage. (4) Uric acid metabolism was not affected by dexamethasone, although the drug was clinically effective in the one case of gout. (5) Calcium and phosphorus balance studies (3 cases) showed either no effect or only a moderate increase in urinary elimination. (6) Dexamethasone caused a significant reduction in the urinary excretion of 17-ketosteroids and 17-hydroxysteroids [number of cases not stated], while other hormonal effects included the production of a Cushing-like syndrome. (7) The number of circulating eosinophil granulocytes fell in cases in which previous treatment had not already influenced the initial count [in an unstated proportion of 6 cases].

Max Mayer

612. **Two-year Comparative Study of Serial Hemagglutination Tests Done on Groups of Rheumatoid Arthritis Patients**

G. K. DE FOREST, M. B. MUCCI, and P. L. BOISVERT. *Arthritis and Rheumatism* [*Arthrit. and Rheum.*] **1**, 387–391, Oct., 1958. 1 fig., 6 refs.

In a previous paper from the Grace–New Haven Community Hospital and Yale University of Medicine (de Forest *et al.*, *Amer. J. Med.*, 1956, **21**, 897) it was reported that in 10 out of 15 cases of rheumatoid arthritis undergoing a Grade-I remission the agglutination reaction with sensitized sheep erythrocytes had become negative. Shortly afterwards the reaction became negative in 4 more of these cases. This group has now been observed for a further 2-year period and the behaviour of the reaction compared with that in 2 other selected groups of cases of the same disease in which it followed a different clinical course.

Of the original group of 15 patients, 11 have remained in complete remission and in 10 of these the haemagglutination reaction has remained negative. Four patients suffered clinical relapse and developed a positive haemagglutination reaction; 3 of these again went into remission and in 2 the reaction once more became negative. The first of the two contrasting groups was a series of 25 patients with consistently progressive chronic rheumatoid arthritis who had had no remission for 2 years previously and had none during the 2 years of observation. In this group the reaction was consistently positive in moderately high titre (1:128 to 1:512) except that in 2 cases a negative result was obtained on one

occasion only and without apparent relation to the clinical status. The second contrasting group consisted of 25 patients with either monarticular arthritis or very mild fluctuating polyarthritis who were diagnosed as having "possible rheumatoid arthritis". Of this group, all but one gave negative haemagglutination reactions. In 2 cases the condition progressed to typical rheumatoid arthritis, though the negative reaction was maintained.

It is suggested that serial determinations of the haemagglutination reaction have a significance which the single isolated determination does not possess. Broad differences in the pattern of reaction can be distinguished when cases are grouped clinically. In the difficult category of "possible rheumatoid arthritis" the results are not generally diagnostically helpful. Conversion of the reaction from negative to positive occurs fairly promptly in individuals whose disease becomes reactivated, but the conversion from positive to negative during remission may take several months. Minor fluctuations in the clinical course are not reflected in changes of titre.

Harry Coke

613. **The Latex Fixation Test in Rheumatoid Arthritis**
G. BURBY and G. BEHR. *Lancet* [*Lancet*] **2**, 1157–1158, Nov. 29, 1958. 3 refs.

The latex fixation test of Singer and Plotz and a modification using bovine γ-globulin are described. Both tests were found to be as sensitive and specific as the Waaler–Rose test.—[Authors' summary.]

614. **Prevalence of Rheumatoid Arthritis in Urban and Rural Populations in South Wales**
W. E. MIALL, J. BALL, and J. H. KELLGREN. *Annals of the Rheumatic Diseases* [*Ann. rheum. Dis.*] **17**, 263–272, Sept., 1958. 2 figs., 21 refs.

To determine and compare the incidence of rheumatoid arthritis in an urban and in a rural area of South Wales surveys of the adult population were carried out in 1953 and 1955 by the Medical Research Council's Pneumoconiosis Research Unit and the Rheumatism Research Centre of the University of Manchester. The areas chosen were the Rhondda Fach, a densely populated mining valley with an adult population of about 20,000, and the neighbouring Vale of Glamorgan, an agricultural area (including a small market town) with an adult population of about 4,600. After a private census had been taken 90% of the population in the former and 95% in the latter area attended a centre for chest radiography, when they were questioned about rheumatic symptoms. The information so obtained, together with data from rheumatic clinics and general practitioners, permitted a list to be made of potential rheumatic subjects, all of whom were then visited by a physician. Those with a history or physical signs suggestive of present or past rheumatoid arthritis were asked to attend a centre for further investigation. Standardized diagnostic criteria were adopted for the interpretation of radiographs of the hands and feet, all films being read by the same observer, and sheep-cell agglutination tests for rheumatoid arthritis were carried out in one laboratory by the method of Ball (*Lancet*, 1950, **2**, 520; *Abstr. Wld Med.*, 1951, **9**, 425), agglutination at a titre of at least 1:32 after 18 hours' incubation being accepted as a positive result. No defined standards were used for clinical diagnosis, but no such diagnosis was accepted unless confirmed by radiological or serological evidence of rheumatoid arthritis, or both. Of the total of 474 suspected cases (282 in the Rhondda Fach, 192 in the Vale of Glamorgan), 391 (82%) were examined both radiologically and serologically, while 58 others underwent one or other investigation.

The over-all incidence of confirmed rheumatoid arthritis in both areas was about equal for the two sexes, but was lower in young females than in young males. In the Rhondda Fach the maximum incidence (1·3%) for males occurred between 45 and 55 years, the rate then declining to 0·9% at 65 and over; for females the maximum (2·0%) was at 55 to 65 years, after which the rate fell to 1·2%. In the Vale of Glamorgan, however, the highest incidence in both sexes (4%) occurred among those over 65 years of age, the incidence at age 45 to 55 in males being 0·7% and in females 0·5%, both rates rising steeply thereafter. Thus the prevalence of rheumatoid arthritis, according to the strict criteria adopted, was higher in the urban than in the rural population, except in the oldest age groups. Moreover, it is stated that "for each radiological grade of severity of arthritis, the sheep cell agglutination test was positive at greater dilutions in urban than in the rural subjects".

The authors note that their findings are contrary to accepted clinical experience and "obviously need further investigation". The possibility that certain types of rheumatoid disease were excluded by their adoption of unusually strict criteria is mentioned, and the significance of asymptomatic radiological and serological findings in subjects over 65 discussed. The desirability of further surveys of random populations is stressed.

V. Reade

615. **Familial Occurrence of the Rheumatoid Factor**
M. ZIFF, F. R. SCHMID, A. J. LEWIS, and M. TANNER. *Arthritis and Rheumatism* [*Arthrit. and Rheum.*] **1**, 392–399, Oct., 1958. 1 fig., 24 refs.

Although possession of the rheumatoid factor in the serum has been shown to be a fairly specific attribute of patients with rheumatoid arthritis, false positive reactions occur in a small proportion of cases in both agglutination and agglutination-inhibition tests with sensitized sheep erythrocytes and in the latex fixation test. In view of the evidence for a familial tendency in rheumatoid arthritis the authors decided to study the incidence of such positive results among members of the families of patients with rheumatoid arthritis compared with that in non-rheumatic subjects. In this paper from New York University College of Medicine they record the result of tests on two groups of relatives of patients with rheumatoid arthritis. In the first group, consisting of 140 relatives (44 parents, 36 offspring, and 60 siblings) of 46 patients, the euglobin fraction of the serum was examined by the agglutination and agglutination-inhibition techniques (Ziff *et al.*, *Amer. J. Med.*, 1956, **20**, 500; *Abstr. Wld Med.*, 1956, **20**, 387) and similar tests were carried out on 140 control subjects, none of whom had a personal or family history suggesting

rheumatoid arthritis. Of the relatives, 16 had rheumatic symptoms and were excluded from the comparison with the control series. Of the remaining 124 asymptomatic relatives, 21 (16·9%) gave a positive haemagglutination-inhibition reaction compared with 7 (5·0%) of the control subjects. In 19 (41%) of the 46 families tested at least one member gave a positive result. There was no significant variation in the incidence of positive reactions with age or sex, but symptoms were more common in female relatives than in males. The second group consisted of 71 relatives of 32 patients, 24 of the families having also been members of the first group. Each was matched with a control subject of the same sex and, with 10 exceptions, of the same age within 2 years, and the capillary-tube latex fixation test of Tanner and Ziff (*Arthrit. and Rheum.*, 1958, **1**, 376) performed on both. Of the 67 asymptomatic relatives, 8 (11·9%) gave a positive result compared with 1 (1·4%) of the 71 control subjects.

Although these findings indicate that a substance with the properties of the rheumatoid factor occurs significantly more frequently in the serum of the healthy siblings, parents, and offspring of patients with rheumatoid arthritis than among control subjects from non-rheumatic families, the authors do not suggest that the available evidence is sufficient to show that the rheumatoid factor itself is inherited, since the increased agglutinating activity demonstrated may result from an increase in concentration of some normally occurring agglutinating substance. *Harry Coke*

616. **Use of the Intramuscular Route for Prednisolone Acetate Therapy**

H. F. West. *Annals of the Rheumatic Diseases* [*Ann. rheum. Dis.*] **17**, 273–277, Sept., 1958. 1 fig., 1 ref.

Since the oral administration of prednisolone may be interrupted by, or may be the cause of, gastro-intestinal disturbance and may possibly also upset liver function, while the sudden withdrawal of the drug may have unpleasant results, the author has tried the effect of intramuscular injections of prednisolone acetate suspension (P.A.I.M.; "deltacortril") with the aim of obtaining a more prolonged action in 16 patients with rheumatoid arthritis selected from some 4,000 cases treated at the Centre for Rheumatic Diseases, Sheffield. The ages of the patients, 7 men and 9 women, ranged from 34 to 62, and 10 were suffering (in addition to the rheumatoid arthritis) from digestive disturbance (including 2 with duodenal ulcer and 3 with gastric haemorrhage), 2 from myxoedema, 2 from bronchitis, and one from thyrotoxicosis. The dosage of P.A.I.M. ranged from 25 to 100 mg., and the injections were given either weekly (7 cases), or initially daily (2), on alternate days (4), or every third day (3), depending on the need of the patient.

The results varied from case to case. Thus a dose of 25 mg. of P.A.I.M. produced a therapeutic effect within 3 to 4 hours in a patient needing little added steroid, whereas another who had been maintained on 15 mg. of oral prednisolone daily suffered a temporary relapse when given 25 mg. intramuscularly until a cumulative effect was produced after 3 or 4 days. The length of time a depot dose remained effective depended on the size of a dose and also on the need of the patient, as determined clinically and by estimation of the urinary corticosteroid excretion. For example, a previously untreated patient excreting only 7 mg. of total 17-hydroxycorticosteroids daily benefited for 6 to 9 days from a single dose of 100 mg. of P.A.I.M., but another requiring 15 to 20 mg. of prednisolone orally had to have the above dose repeated every 3rd, 4th, or 5th day. Patients with disease of average severity did well on a dose of about 80 mg. of P.A.I.M. per week. All digestive disturbances were relieved (although 3 had later a relapse), and no new gastro-intestinal upsets developed in patients previously free. Improvement in the arthritis sufficient to permit return to work or freedom from symptoms was achieved in 11 cases, and some improvement in the remainder. The author has no doubt that prednisolone given intramuscularly is of real value in avoiding the gastro-intestinal disturbances that occur with oral therapy. He concludes that it remains to be seen whether prednisolone given by this route will remain effective for a longer time than oral prednisolone. *V. Reade*

SYSTEMIC LUPUS ERYTHEMATOSUS

617. **Clinical Diagnosis of Systemic Lupus Erythematosus**

R. Armas-Cruz, J. Harnecker, G. Ducach, J. Jalil, and F. Gonzalez. *American Journal of Medicine* [*Amer. J. Med.*] **25**, 409–419, Sept., 1958. 34 refs.

The authors present a review of the findings in 108 cases of systemic lupus erythematosus (L.E.) admitted to the Hospital San Juan de Dios, Santiago, Chile. Arthralgia or arthritis of the upper extremities was found in 91% of cases, and classically responded to steroid therapy (cortisone); joint deformity was rare. Among the other features were protean and pleomorphic rashes, including a psoriatic form, but particular emphasis is laid on the presence of alopecia and the characteristic, thin, lustreless "lupus hair". Chemosis and nail-bed telangiectasis were considered to be useful diagnostic features. Gastro-intestinal symptoms were common but non-specific; hepatitis was frequently present, but was indistinguishable from other forms of hepatitis. A dominant feature was involvement of the serous cavities, the pleural cavity being involved unilaterally or bilaterally in 56% of the cases; L.E. cells, however, were not found in the pleural exudates. Cardiac involvement, as manifested by tachycardia, triple rhythm, endocardial and exocardial murmurs, was noted in 88% of the patients. Libman–Sacks verrucous endocarditis, which is pathognomonic of the disease, produces no clinical signs, and is purely a post-mortem finding. Splenomegaly occurred in 19% of cases and was occasionally associated with either thrombocytopenia or haemolytic anaemia. Various clinical syndromes, including cranial nerve palsies and myelitis, were noted as the result of involvement of the central nervous system. In 15% of these cases systemic lupus erythematosus had been preceded by Raynaud's phenomenon.

Laboratory investigations, which are described in some detail, confirmed the almost specific nature of the L.E.-cell test in experienced hands; the reaction was positive in 90·4% of cases in this series, although it was negative in a few cases in which the presence of L.E. was confirmed at necropsy. An increased erythrocyte sedimentation rate and serum γ-globulin level were found with the usual frequency. Renal function tests revealed renal involvement in 76% of the cases, although serious azotaemia was relatively uncommon.

[Although this communication adds little that is new to our knowledge of this disease, it is nevertheless a useful retrospective analysis.] *J. N. Harris-Jones*

618. **Clinical Application of a Test for Lupus Globulin–Nucleohistone Interaction Using Fluorescent Antibody**
G. J. Friou. *Yale Journal of Biology and Medicine* [*Yale J. Biol. Med.*] **31**, 40–47, Sept., 1958. 1 fig., 12 refs.

The author has previously demonstrated by the fluorescent antibody technique that a globulin factor in serum from patients with disseminated lupus erythematosus (D.L.E.) reacts with the nucleoprotein component of cell nuclei (*J. Immunol.*, 1958, **80**, 324; *Abstr. Wld Med.*, 1959, **25**, 2). The activity of such sera can be titrated against a nucleohistone extract of calf thymus, and in this further paper from the Veterans Administration Hospital, West Haven, Connecticut, and Yale University School of Medicine a technique developed for this purpose is described and the results obtained with sera from 369 patients with various diseases are reported.

The test gave a positive result with all of 35 sera from patients with D.L.E. Positive results were also obtained in 4 of 42 cases of rheumatoid arthritis, 1 of 3 cases of scleroderma, 1 of 2 cases of dermatomyositis, 4 of 17 cases of chronic biological false positive reaction to serological tests for syphilis, and 1 of 16 cases of drug-sensitivity rashes. Sera from 5 patients with discoid L.E. gave negative results. Of the other sera tested, positive results were obtained only with 2 from patients considered to have latent syphilis (though since the treponemal immobilization test had not been performed the possibility of biological false positive reactions could not be excluded) and one from a patient with advanced bronchogenic carcinoma. The positive reactions with sera from patients considered not to have D.L.E. were of relatively low titre with the exception of 2 cases of rheumatoid arthritis, in both of which there were features suggestive of D.L.E. In cases of D.L.E. the titre tended to be high during periods of acute illness, but relatively low during remissions. *M. Wilkinson*

619. **Latex Agglutination Test for Disseminated Lupus Erythematosus**
C. L. Christian, R. Mendez-Bryan, and D. L. Larson. *Proceedings of the Society for Experimental Biology and Medicine* [*Proc. Soc. exp. Biol. (N.Y.)*] **98**, 820–823, Aug.–Sept., 1958. 9 refs.

Recent studies by various workers have shown an interaction between the serum of patients with disseminated lupus erythematosus (D.L.E.) and whole nuclei or nucleoprotein, demonstrable by immunofluorescence, complement fixation, or agglutination of nucleoprotein-coated sheep cells. The present paper, from the Presbyterian Hospital (Columbia University), New York, describes how latex particles coated with nucleoprotein from the calf thymus were agglutinated by most D.L.E. sera tested. Because occasional sera, notably from patients with rheumatoid arthritis, agglutinated uncoated latex, all sera which agglutinated nucleoprotein latex were checked against uncoated latex.

It was found that a positive reaction against nucleoprotein-coated latex was given by sera from 19 out of 24 patients with D.L.E. who had at some time shown a positive L.E.-cell test reaction and 2 out of 6 sera from patients with probable D.L.E. (but a negative L.E.-cell reaction). No agglutination occurred with sera from 4 patients with discoid L.E., 50 with rheumatoid arthritis, or 84 patients with other diseases. However, the sera of 3 further patients with rheumatoid arthritis and of one patient each with multiple myeloma and chronic renal disease showed agglutination with both uncoated and nucleoprotein-coated latex. It was further shown that agglutination of nucleoprotein-coated latex was inhibited by previous exposure of a positive D.L.E. serum to deoxyribonucleic acid, but not by exposure to ribonucleic acid, deoxyribose, or histone. In 2 cases the absorption of positive D.L.E. sera with nucleoprotein-coated latex markedly reduced or abolished their agglutination titre and reversed a positive L.E.-cell test reaction in each case. The authors consider that this test is valuable in the diagnosis of D.L.E., and particularly in differentiating it from rheumatoid arthritis. *M. Wilkinson*

620. **Systemic Lupus Erythematosus. Results of Treatment with Triamcinolone**
E. L. Dubois. *California Medicine* [*Calif. Med.*] **89**, 195–203, Sept., 1958. 1 fig., 11 refs.

A series of 29 patients with systemic lupus erythematosus were treated with triamcinolone at the Los Angeles County General Hospital for an average of 4 months. The usual maintenance dose necessary to control mild exacerbations was 26 mg. a day. No prophylactic measures against the development of peptic ulcer were taken except when specifically indicated. Of 16 patients who underwent periodic x-ray examination, only one, who was receiving 96 mg. daily, was shown to develop a peptic ulcer. Serial histamine test meals in 9 cases revealed no abnormality. The clinical manifestations of the disease were suppressed in the same way by triamcinolone as by the older steroids, though long-standing renal involvement was not affected. During treatment with triamcinolone there was progressive loss of weight, and cutaneous side-effects such as Cushingoid appearance, striae, and hirsutism were more marked than with other steroids. In 6 cases profound muscle weakness, particularly of the quadriceps group, occurred.

The author concludes that since triamcinolone is more liable to produce cutaneous side-effects than the older hormones, it cannot be regarded as the drug of choice for beginning therapy in the average case of systemic lupus erythematosus. *Oswald Savage*

Neurology and Neurosurgery

621. **Critical Flicker Frequency and EEG Findings in Patients with Brain Damage**
K. A. KOOI, R. S. BOSWELL, and M. H. THOMAS. *Neurology* [*Neurology* (*Minneap.*)] **8**, 764–768, Oct., 1958. 13 refs.

In this study reported from the University of Utah College of Medicine, Salt Lake City, the results of tests for flicker-fusion frequency were correlated with those of electroencephalographic (EEG) studies in 60 normal subjects, 19 psychiatric patients without neurological damage (14 with schizophrenia), and 54 patients with organic brain damage, comprising 18 with intellectual impairment only, 25 with organic damage other than ocular, and 11 with organic damage including ocular damage (optic atrophy, glaucoma, cataract, and retinitis). The method of testing for flicker-fusion frequency is described in detail.

Flicker-fusion frequency was significantly higher in the control group (32 c.p.s.) than in any of the other groups, and was also significantly higher in the psychiatric group (28·5 c.p.s.) than in the 3 groups with organic damage, for which the values were 25·5, 25, and 22·5 c.p.s. respectively. A flicker-fusion frequency of less than 25 c.p.s. is considered to be highly suggestive of organic brain damage, no subject in the normal control group having a rate as low as this. Comparison with the EEG results showed that patients with brain damage who had a normal EEG, or even an abnormal EEG but with occipital frequencies within the normal range, had a significantly higher mean flicker-fusion frequency (27 c.p.s.) than the remainder (mean 23 c.p.s.). No correlation was found between flicker-fusion frequencies and alpha frequencies or the responses to photic stimulation.

Brodie Hughes

622. **Cluster Headache**
A. P. FRIEDMAN and H. E. MIKROPOULOS. *Neurology* [*Neurology* (*Minneap.*)] **8**, 653–663, Sept., 1958. 16 refs.

The authors discuss the nature and treatment of "cluster" headaches, so named because the attacks usually occur in groups or clusters. The pain, which is referred to the region of the orbit or temple unilaterally, is stabbing in character and is often described as agonizing. It may be associated with ipsilateral injection of the conjunctiva, with lacrimation, and with stuffiness of the nose.

It appears that the syndrome has been described frequently in the literature under a variety of names, of which the most recent is "histaminic cephalalgia"; it has usually been regarded as a variant of migraine, but numerous theories have been propounded as to its origin and mechanism. It is generally agreed that dilatation of the extracranial branches of the external carotid artery is responsible for the local flushing and feeling of fullness, but this would not account for the photophobia, lacrimation, and scotomata. To explain the vasodilatation lesions of the sphenopalatine ganglion and superficial petrosal nerve have been postulated, while a local release of histamine has also been suggested to account for the symptoms, but the results of treatment with antihistaminics do not bear this out.

In a series of 50 cases studied by the authors at Montefiore Hospital, New York, the patients' average age was 28 years and males predominated in a ratio of 4·5 to 1. Psychologically, the subjects were typically predisposed to sustained emotional states and with a tendency to compulsive behaviour. The duration of disease averaged 12·8 years, but ranged as widely as 2 to 37 years. No past history of allergy, injury, or disease was elicited in any significant number of cases. In this series the paroxysm lasted from 30 minutes to 2 hours and each cluster or bout for 4 to 10 weeks, with intervals of 7 to 18 months between bouts. Prodromata were rare. In the differential diagnosis the location of the pain in the orbital region, the presence of lacrimation, absence of visual disturbances, and absence of prodromata were the chief features helping to distinguish this condition from migraine.

Ergotamine preparations are of some value in treatment, parenteral administration giving the best results. The authors found suppositories of "cafergot" containing 2 mg. of ergotamine tartrate and 100 mg. of caffeine more effective than oral preparations.

William Hughes

623. **Horner's Syndrome: an Analysis of 216 Cases**
C. L. GILES and J. W. HENDERSON. *American Journal of Ophthalmology* [*Amer. J. Ophthal.*] **46**, 289–296, Sept., 1958. 1 fig., 23 refs.

The classic features of Horner's syndrome are miosis, ptosis of the upper lid, anhidrosis, and enophthalmos, all on the affected side. The syndrome is the result of interruption of the sympathetic pathways of the autonomic nervous system at any point in their course from the hypothalamus to the orbit. The present authors describe this three-neurone pathway and report a study of 216 cases of Horner's syndrome seen over a period of 21 years at the University Hospital, Ann Arbor, Michigan, the object of the study being to determine as nearly as possible the anatomical sites of sympathetic interruption and the aetiological factors involved.

The most common site of interruption of the sympathetic pathway to the eye is in the sympathetic trunk and in the post-ganglionic fibres before they course intracranially. The upper thoracic and lower cervical anterior spinal roots are affected less than half as frequently as the sympathetic trunk, while the brain stem, spinal cord, and intracerebral post-ganglionic fibres are rarely affected. Neoplasia, malignant more often than benign, is the most common aetiological agent; bronchogenic and metastatic carcinomata are the most common

tumours, and neurofibroma and thyroid adenoma are the only significant benign tumours. Surgical procedures, non-operative trauma, and vascular disease are less important causes of Horner's syndrome.

Neoplasia is the predominant factor in sympathetic trunk lesions, while trauma and vascular disease are most frequently encountered " at the anterior spinal root and brain stem levels respectively. Spinal cord sympathetic pathway interruption was most commonly a result of trauma. Herpes zoster was the only condition implicated in an intracranial post-ganglionic lesion. Horner's syndrome is seen most commonly in older age groups. In the first two decades of life trauma is the most common cause. Malignant and benign neoplasms account for the largest percentage of sympathetic interruptions in the third, fourth, and fifth decades."

In view of the fact that the lesions producing Horner's syndrome are often serious, a complete investigation should be carried out, including examination of stereoscopic and lateral radiographs of the chest and radiographs of the skull and lateral cervical and upper thoracic vertebrae, together with detailed neurological examination. If there is any suspicion of a spinal-cord tumour myelography should also be carried out.

J. MacD. Holmes

BRAIN AND MENINGES

624. **Asterixis. Its Occurrence in Chronic Pulmonary Disease, with a Commentary on Its General Mechanism**
H. O. CONN. *New England Journal of Medicine* [*New Engl. J. Med.*] **259**, 564–569, Sept. 18, 1958. 45 refs.

Asterixis, which is commonly known as " liver flap ", means literally the inability to maintain a fixed posture. The sign is elicited by asking the patient to extend his arms and dorsiflex his hands for several minutes, whereupon a series of sudden, rapid, flexion–extension " flapping " movements appear at the wrist. It was first described by Adams and Foley (*Trans. Amer. neurol. Ass.*, 1949, **74**, 217) in association with severe hepatic disease, but within a few years it was reported in a variety of non-hepatic disorders, including pulmonary insufficiency, the malabsorption syndrome, hypomagnesaemia, uraemia, polycythaemia with congestive heart failure, hypopotassaemia, and bromism. It may be precipitated in cirrhotic patients by the administration of a high-protein diet, ammonium chloride, acetazolamide, methionine, and chlorothiazide. The most common non-hepatic disease in which asterixis has been reported is pulmonary insufficiency with cardiac decompensation, and the author describes 6 further such cases seen at the Grace–New Haven Community Hospital, New Haven, Connecticut.

He considers that the wide variety of clinical disorders in which asterixis has been observed suggests that it is a non-specific phenomenon of limited diagnostic value, and that it can be produced by any of a variety of metabolic and mechanical disturbances which impair brain metabolism. He advocates that the term " liver flap " should be discarded in favour of " flapping tremor " or asterixis.

T. Semple

625. **Treatment of Severe Head Injuries**
I. N. MACIVER, L. P. LASSMAN, C. W. THOMSON, and I. MCLEOD. *Lancet* [*Lancet*] **2**, 544–550, Sept. 13, 1958. 4 figs., 19 refs.

The authors review the 82 cases of severe head injury seen at the General Hospital, Newcastle upon Tyne (5·5% of all such cases) between Jan. 1, 1955, and Dec. 11, 1956, which were characterized by partial or complete decerebrate rigidity, tonic fits, and a rapidly rising temperature. Such a clinical picture indicates either primary intrinsic midbrain injury or secondary damage in this area occasioned by a pressure cone resulting from a rise in supratentorial pressure. Haemorrhage, either extradural or subdural, is the commonest cause of such increased pressure and this was present in 42 of the cases reviewed; but hyperaemia and oedema of the brain secondary to the trauma itself, as well as hypoxia and carbon dioxide retention, will further increase the intracranial pressure, while a rise in venous pressure such as occurs with respiratory embarrassment may aggravate the condition. The other clinical features of these cases, for which the prognosis is grave, are summarized, and the treatment recently described by Maciver *et al.* (*Lancet*, 1958, **1**, 390; *Abstr. Wld Med.*, 1958, **24**, 140), of which one of the main objects is to combat respiratory insufficiency and cerebral anoxia, is recalled. In these cases the authors give no food by mouth until they consider that the risks of regurgitation have passed, that is for 1 to 4 weeks. During this period the patient receives intravenous fluids only, these being made hypertonic with 50% glucose or sucrose for the first week after injury. The serum electrolyte concentrations are determined regularly. After this initial period of 1 to 4 weeks feeding by tube is begun and continued until the tracheotomy performed soon after admission is closed. Appropriate antibiotic therapy is instituted.

The 82 cases reviewed consisted of a control group of 56 cases (collected in retrospect from the records) which had not been treated by the regimen outlined and 26 cases which were so treated. Among the control group of patients the mortality was 69·6% (39 deaths), whereas in the treated group it was only 38·4% (10 deaths). As regards residual disability, of the 17 survivors in the control series, 10 made a good recovery, 3 had a severe neurological deficit, 3 were paralysed and were totally dependent, while one suffered a severe personality change and was " difficult to manage "; of the 16 survivors in the treated group, 11 made a good recovery, but 5 showed some degree of neurological defect and/or a defect of intellect and personality.

J. E. A. O'Connell

626. **Ocular Signs and Prognosis in Subdural and Subarachnoid Bleeding in Young Children**
R. W. HOLLENHORST and H. A. STEIN. *A.M.A. Archives of Ophthalmology* [*A.M.A. Arch. Ophthal.*] **60**, 187–192, Aug., 1958. 17 refs.

In this paper from the Mayo Clinic the authors discuss the ocular findings in 47 cases of proved subdural haematoma, subdural hygroma, and subarachnoid haemorrhage occurring in children under the age of 5 years. Ocular abnormalities—predominantly massive retinal

and subhyaloid haemorrhages—were present in 28. Palsy of the extraocular muscles and papilloedema were also observed. The prognosis as regards impairment was poor in the patients with ocular damage, 8 out of 23 traced having permanent ocular defects compared with one out of 15 without ocular damage. The authors were unable to find any ophthalmoscopic features which would permit subdural haemorrhage to be distinguished from subarachnoid haemorrhage.

C. Skelton Smalley

627. **Glioblastoma Multiforme. Review of 219 Cases with Regard to Natural History, Pathology, Diagnostic Methods, and Treatment**
S. A. FRANKEL and W. J. GERMAN. *Journal of Neurosurgery* [*J. Neurosurg.*] **15**, 489–503, Sept., 1958. 8 figs., 10 refs.

An unselected series of 219 cases of glioblastoma multiforme has been reviewed from the standpoint of natural history of the disease, diagnostic studies, treatment, and pathology.

Natural history. The sex incidence was 58% males and 42% females. The age incidence was greatest in the fifth and sixth decades. The total duration of the disease was under a year in 67% of the cases; 11% of the patients, however, lived 2 to 5 years. The duration was not related to the age or sex of the patient. The duration of symptoms prior to diagnosis was less than 6 months in 70% of the cases but 17% of the patients had histories longer than a year. The frequency of various symptoms is tabulated. Headache was most common. Seizures occurred in a third of the cases and were the initial symptom in half of these. There was no evidence of familial incidence nor of a relationship with any other disease of the nervous system.

Diagnostic studies. The cerebrospinal fluid is almost always abnormal in some respect. There was a mortality rate of 2% for the procedure of lumbar puncture while the information gained was nonspecific. Routine use of this procedure is not recommended. Roentgenograms of the skull were abnormal in 59% of the cases. Electroencephalograms were abnormal in 93% and localized the lesion correctly in 49% of the cases. Pneumoencephalograms were done only 19 times with one fatality. The lesion was localized in only 3 cases. Ventriculograms gave a correct localization in 77% of 135 cases. Arteriography was performed in only 21 cases with 48% successful localization.

Treatment. There were 183 patients treated surgically, with an operative mortality of 18·5%. Average postoperative survival was about 3 months. The more radical surgical procedures, including " total " removal of the tumor and lobectomy, offered the best prognosis with regard to operative mortality and survival time. Of 47 patients receiving radiotherapy, 21 received a course of 2,700–5,900 r tumor dose completed within 60 days after operation. This group showed a significantly higher percentage of survivors during the first year when compared with a group who had surgery alone. The effect of all present forms of treatment is to prolong life by 3 to 6 months. Long-term survivals are just as common among untreated patients as those treated. Postoperative disability tended to be great. Only 40% of the patients had slight or no disability. There was no remission of symptoms in 60% of the cases. Only 15% of the patients went 6 months without a recurrence. There were no cures.

Pathology. The anatomical site, and gross and microscopic characteristics of these tumors are tabulated. The number of mitotic figures seen is shown to bear no relationship to prognosis.—[Authors' summary.]

628. **Long-range Effects of Electropallidoansotomy in Extrapyramidal and Convulsive Disorders**
E. A. SPIEGEL, H. T. WYCIS, and W. H. BAIRD III. *Neurology* [*Neurology (Minneap.)*] **8**, 734–740, Oct., 1958. 1 fig., 24 refs.

The authors report the results of a long-term follow-up of patients treated for various neurological conditions by stereotaxic operations on the basal ganglia. In the majority of cases areas of the pallidum and ansa lenticularis were electrically coagulated, while in some epileptic patients additional coagulation was produced in the amygdaloid nucleus. The operations were carried out under local anaesthesia whenever possible so that the effects of both stimulation and coagulation on the symptoms and signs of the disorder could be assessed.

Of 50 patients aged 19 to 79 years suffering from post-encephalitic Parkinsonism or paralysis agitans of 3 to 34 years' duration subjected to 71 operations (bilateral in 9 cases) and followed up for one to 6 years, the tremor, which had been unresponsive to medication, was abolished or greatly reduced in 22 (44·9%) and was moderately improved in 16 (32·6%). In 6 cases, however, the tremor recurred a few days to 20 months after operation; it was noted that these were patients in whom the lesion had been made anteriorly in the pallidum, either at the level of the anterior commissure or 3 mm. posterior to it, and when in 5 of these the lesion was enlarged posteriorly up to 9 mm. behind the anterior commissure the tremor was abolished in 4 and reduced in one. Duration of the disease seemed to bear little relation to the result, but the patient's age was important, good results being obtained in about half of those under 50 but only one-quarter of those over 60 being improved. Rigidity, which was a marked feature in 36 of the patients, was greatly reduced in 26 (72·2%). There was no relationship between this result and age or duration of the disease. There were 2 deaths, these occurring in one patient who developed postoperative hemiplegia and died 4 months later and in another who died of congestive heart failure and pneumonia after a second operation. Permanent hemiplegia occurred in 2 cases (4%) and transient parésis in 6 (12%). These complications were commonest among the older patients. Complete rehabilitation enabling the patient to resume previous employment was obtained in 9 cases (18%) and partial rehabilitation in 15 (30%). The degree of rehabilitation was closely related to the patient's age and previous disability.

Among the patients treated for other extrapyramidal conditions there were 4 with Huntingdon's chorea, the involuntary movements being abolished in one and reduced in 2; but 2 patients with other types of chorea

were unchanged. In patients with athetosis the authors consider it advisable to test the probable effects of coagulation by giving a preliminary injection of procaine, as there is a possibility of making the condition worse by pallidotomy. In one case of post-hemiplegic athetosis the movements were abolished and in 2 of double athetosis improvement was obtained on the worse side by a unilateral operation, but in 2 cases of cerebral palsy with athetosis only slight improvement was obtained, while of 2 cases of torsion dystonia, one was greatly improved and the other slightly improved. The results of treatment of spastic lesions were variable; in 2 cases of hemiplegia no reduction in spasticity was noted, but in a third case in which a sudden hemiplegia had followed ectopic pregnancy the spasticity was greatly reduced following operation, and tonic innervation, which had been a particularly disabling feature, was abolished. Lastly, of 12 patients with epilepsy (5 treated by pallidotomy and 7 by pallidotomy and amygdalotomy) after follow-up for periods of 6 months to 2 years the attacks were controlled or markedly reduced in 7 (58·3%), but in the remainder the results were unsatisfactory in that the attacks were unchanged or returned after temporary improvement; in all but 2 of these cases, however, the operation was unilateral only. So-called "salaam" seizures were most favourably affected, being abolished in 5 out of 8 cases and greatly reduced in number in one.

Brodie Hughes

CRANIAL NERVES

629. A Study of the Treatment of 637 Patients with Trigeminal Neuralgia

D. RUGE, R. BROCHNER, and L. DAVIS. *Journal of Neurosurgery* [*J. Neurosurg.*] **15**, 528–536, Sept., 1958.

On the basis of observations on a series of 637 patients treated for trigeminal neuralgia since 1920, the authors of this paper from the Northwestern University Medical School, Chicago, present a study of the symptomatology of the condition and an evaluation of the various forms of treatment. Some well-known findings were confirmed —namely, the more frequent occurrence of trigeminal neuralgia in females, the rather more frequent involvement of the right side of the face than the left, and the relative infrequency of bilateral involvement. Pain starting in or limited to the ophthalmic division was found to be rare. The age of onset of pain in these 637 patients varied from 15 to 89 years (average 51 years). Spontaneous remission lasted 18 months or more in 21 patients, and 2 patients were free from pain for 7 years. Diseases found in association with trigeminal neuralgia included disseminated sclerosis (14 patients, one of whom had bilateral involvement); meningioma of the dural envelope of the Gasserian ganglion (6 patients); cerebrovascular accident at the onset of pain (3 patients); and carcinoma of the antrum, pernicious anaemia, cryptogenic epilepsy, and herpes zoster (each in one patient); a positive Wassermann reaction was obtained in 3 cases.

Injections of alcohol into the Gasserian ganglion or the peripheral branches of the trigeminal nerve had been given at some time to 298 patients to a total of 821 such injections, 503 of which gave relief lasting on the average 7·2 months. In some cases relief following injection had been unusually successful, one patient being free from pain for 25 years afterwards. The various complications of alcohol injections encountered are described. Avulsion of peripheral branches of the trigeminal nerve had also been performed 13 times before the patients came under the care of the authors, with relief for periods varying up to 2 years.

In 627 cases in the series the authors performed extradural preganglionic trigeminal neurotomy as described by Frazier and Adson. Of these, 513 have been followed up continuously and the results and complications are described. There were 4 operative deaths. All except 6 of the patients obtained relief of pain and 303 had no complications. In the remaining patients complications included paraesthesiae on the affected side, which were described as severe in 25 and mild in 79 patients, and ulceration of the cornea in 25 patients, 6 of whom subsequently required enucleation of the eye. A few patients had ulceration of the nose and excessive watering of the ipsilateral eye. Six patients maintained that they still suffered from intermittent pain similar to that experienced before operation, in spite of complete loss of sensation to pin-prick, touch, and temperature in the area of the trigeminal nerve. The authors state that the motor root was preserved in 206 cases and selective section spared the sensory innervation of the eye in 65. Two patients committed suicide 8 years after operation. Of 16 who developed pain bilaterally, 2 obtained relief from preganglionic root section on the second side.

The authors consider that extradural preganglionic neurotomy is the most effective surgical treatment of trigeminal neuralgia provided the patient is prepared psychologically for the loss of sensation which accompanies permanent relief of pain. In their view corneal ulceration occurs only after direct trauma to an insensitive cornea, and is not the result of a trophic disturbance independent of injury.

[The mass of detail in this paper cannot be abstracted adequately and the original paper should be consulted.]

J. B. Stanton

630. Eye Movements Associated with Myoclonus

J. C. COOPER. *American Journal of Ophthalmology* [*Amer. J. Ophthal.*] **46**, 205–210, Aug., 1958. 3 figs., 9 refs.

After reviewing the literature on myoclonus, the author cites 7 cases of palatal myoclonus seen at the Johns Hopkins and Baltimore City Hospitals and discusses 4 of these in detail. He states that myoclonus denotes rhythmic contractions of the extra-ocular muscles at a rate of 50 to 180 per minute, the movements being oscillatory, equal in excursion, rhythmic, and synchronous with contractions in other structures. The movements are to be distinguished from those of nystagmus. Muscles of the palate are most frequently affected, but the face, tongue, diaphragm, and other muscles may be involved. Myoclonus can result from a variety of lesions which involve the inferior olivary nucleus, red nucleus, and the pathways by which these structures are related.

D. P. Greaves

Psychiatry

631. **Recurrent Urticaria Alternating with Psychosis. Report of a Case**
ENG-KUNG YEH. *Psychosomatic Medicine* [*Psychosom. Med.*] **20**, 373–378, Sept.–Oct., 1958. 24 refs.

The case is reported from the National Taiwan University Hospital, Taipei, Taiwan (Formosa), of a patient who suffered from recurrent attacks of urticaria alternating with psychotic episodes. Although the psychological aspects of urticaria have been extensively studied, no similar case appears to have been recorded previously.

The patient, a 36-year-old married woman, gave a 5-year history of attacks of urticaria interspersed with 3 acute psychotic illnesses. During her early years she had been rejected by her illiterate and ineffectual mother, but was always closely identified with her austere, intellectual father, who was a schoolteacher. Her marriage at the age of 22 was an arranged one and was marked by psychosexual dissatisfaction and infidelity on the part of both partners. The initial bout of urticaria occurred at the age of 31, when the patient's mother-in-law accused her of neglecting her responsibilities. Shortly afterwards she developed a paranoid hallucinatory illness following a similar accusation by a neighbour. During the psychosis she was free from cutaneous disorder, but the latter reappeared when she was recovering from the psychotic episode after receiving electric convulsion and modified insulin therapy. Another paranoid episode took place later in similar circumstances, and still later she had a severe depressive illness which was ushered in by a suicidal attempt. The urticaria was apparent between, but not during, the psychotic episodes.

The discord between her parents during her childhood is considered to be a relevant background to her illness. The patient's choice of male love objects indicated a persistent infantile attachment to her father. During her first psychotic illness she had a delusion of possession by spirits; this symptom was determined partly by a sense of guilt over her infidelity and partly by cultural patterns in the Far East. *A. Balfour Sclare*

632. **Responses to Sensory Stimulation in Certain Psychosomatic Disorders**
J. G. KEPECS, M. ROBIN, and C. MUNRO. *Psychosomatic Medicine* [*Psychosom. Med.*] **20**, 351–365, Sept.–Oct., 1958. 2 figs., 19 refs.

An investigation was carried out at the Michael Reese Hospital, Chicago, into the role of perceptual processes in the causation of psychosomatic disorders. The aim was to study the central effects of stimulation of senses which are less highly intellectualized than the visual and auditory functions. The subjects were 11 patients with rheumatoid arthritis, 10 with asthma, 13 with atopic dermatitis, and 11 with essential hypertension; in each group there was a preponderance of females. Three modes of sensory stimulation were used: (1) stroking the forehead with cotton wool for 2 minutes (skin sensation); (2) holding one arm horizontal for a minute (proprioception); and (3) smelling a special mixture of jasmine and skatol (olfaction). The stimuli were applied to the subjects " in more or less random order " (the olfactory stimulus usually being applied last owing to persistence of the odour). After each stimulus the subject was asked to make a drawing of anything that came to mind, and subsequently discussed the three drawings and their relation to the preceding stimuli with the interviewer. It was assumed that cutaneous stimulation would prove specifically significant to the patients with atopic dermatitis, olfactory stimulation to the asthmatics, and proprioceptive stimulation to the arthritics. The patients with hypertension were chosen as a control group since there was no reason to expect any of the sensory functions tested to be specifically associated with this disorder.

The results of testing confirmed the assumptions in respect of the first three groups and showed, as expected, that the hypertensive group did not react specifically to any of the three stimuli. Independent ratings showed that the strongest affective response was most often evoked by the stimulus particularly relevant to each disorder. As the subjects seldom consciously recognized a connexion between the stimulus on the one hand and the drawing and its associations on the other, it was inferred that the linkage between them occurred at preconscious levels.

It is postulated that, from the perceptual viewpoint, " periphery " and " centre " constitute a complex whose operations may be modified or affected as a unit by the ego. When the influence of the ego is strong, cognitive or intellectualized responses tend to occur; when it is diminished, affective responses predominate.
A. Balfour Sclare

633. **Stress and Disease: a Review of Principles**
D. O'NEILL. *British Medical Journal* [*Brit. med. J.*] **2**, 285–287, Aug. 2, 1958. 11 refs.

634. **Addiction to Unrestricted Drugs**
C. P. SEAGER and A. R. FOSTER. *British Medical Journal* [*Brit. med. J.*] **2**, 950–952, Oct. 18, 1958. 14 refs.

The cases are reported of 7 patients, all female, who had become addicted to drugs obtainable freely in Great Britain without prescription, or the signing of the Poisons Register. The drugs concerned were carbromal (contained in " persomnia ", " dormiprin ", and " somnotil ") (3 cases), chlorodyne (tinctura chloroformi et morphinae, *B.P.C.*) (2 cases), and phenmetrazine hydrochloride (" preludin ") (2 cases). The authors state that all drugs with euphoriant or sedative action are likely to cause addiction, and suggest that such drugs should be placed on the Scheduled List of Poisons *ab initio*, and not only after a number of cases of addiction to them have been reported. *G. S. Crockett*

Dermatology

635. **Oral Treatment of Pruritic Dermatoses with a New Antihistaminic Compound**
R. I. KILE. *Antibiotic Medicine and Clinical Therapy* [*Antibiot. Med.*] **5**, 578–581, Sept., 1958. 8 refs.

Over a period of 1½ years in private practice in Cincinnati, Ohio, a total of 311 patients suffering between them from 32 different forms of itching dermatoses were given tablets of the tannate salts of three antihistamine drugs in combination—phenylephrine, prophenypyridamine, and pyrilamine. With this combination there was said to be controlled continuous release of the drugs. Almost 50% of the patients were judged to have shown a good response; side-effects were negligible.

[No details are given of the duration of treatment or the incidence of relapses; there was no placebo control and the results were not compared with those of other forms of treatment.] *John T. Ingram*

636. **An Appraisal of a New Antipruritic: Trimeprazine ("Temaril")**
L. C. GOLDBERG and A. DIAMOND. *Antibiotic Medicine and Clinical Therapy* [*Antibiot. Med.*] **5**, 582–584, Sept., 1958. 2 refs.

A new antipruritic, trimeprazine, was tried in the treatment of 160 patients of all ages with itching skin eruptions. The dosage of the drug ranged from 2·5 mg. twice a day to 5 mg. every 3 hours. The drug did not affect the dermatosis, but relieved itching effectively in more than 70% of the patients. The best results were obtained in 32 patients with chicken-pox. Side-effects, mostly drowsiness, occurred in 60% of patients. [There were no controls.] *John T. Ingram*

637. **Treatment of Boils with Erythromycin and with Antibiotic E 129**
A. SCOTT. *British Medical Journal* [*Brit. med. J.*] **2**, 83–84, July 12, 1958. 2 refs.

Of 165 patients attending the out-patient departments of St. Bartholomew's Hospital, London, for the treatment of severe boils, 55 were given erythromycin, 250 mg. 4 times daily by mouth for 7 days, 55 received 3 g. daily by mouth of "E 129"—a comparatively new antibiotic related to erythromycin which was described by Garrod and Waterworth (*Brit. med. J.*, 1956, **2**, 61; *Abstr. Wld Med.*, 1956, **20**, 429); the remaining 55, who served as a control group, were treated by the local application of mercury perchloride only.

The evolution of the "boil process" continued for more than 4 days in 22 (40%) of the placebo-treated group, whereas in the 2 antibiotic-treated groups the lesions progressed after this time in only 3 cases. Severe local necrosis with subsequent scarring was observed in 50% of the control group, but in only 3 patients treated with antibiotics. The two antibiotic drugs showed approximately the same ability to arrest the progress of the infection. The boils treated with E 129 healed more rapidly than those treated with erythromycin, 24 (44%) of the former healing within the first week compared with only 16 (29%) of the latter.

Coagulase-positive staphylococci were recovered from 159 of the 165 patients and the rate of occurrence of negative post-treatment cultures was similar in the two antibiotic-treated groups. Diarrhoea associated with the presence of *Candida* in the stools followed erythromycin therapy in 4 patients, but no such complication was observed with E 129. *R. R. Willcox*

638. **Trial of Dequalinium for Skin Infections**
R. B. COLES, C. GRUBB, D. MATHURANAYAGAM, and D. S. WILKINSON. *British Medical Journal* [*Brit. med. J.*] **2**, 1014–1016, Oct. 25, 1958. 3 refs.

A form of treatment for bacterial infections of the skin with minimal risk of sensitization is reported from the Northampton General Hospital and the Aylesbury and High Wycombe Group Hospitals. Dequalinium (decamethylene bis-(4-aminoquinaldinium) chloride), used in the form of a cream (0·4%) or a paint (0·5%), was found not to aggravate non-infectious disorders. It was effective in sterilizing 15 out of 27 cases of coagulase-positive staphylococcal infection within one week, while others were cured after 3 weeks' treatment. It was used with particular benefit in impetigo, folliculitis, neonatal staphylococcal infections, chronic paronychia, and tinea cruris. No irritant or toxic effects were observed, but 3 cases of sensitization (one to the base) occurred.
G. B. Mitchell-Heggs

639. **A Critical Evaluation of the Effect of Steroid Lotions on Inflammatory Dermatoses**
I. L. SCHAMBERG, S. I. ASKOVITZ, and M. GREENBERG. *A.M.A. Archives of Dermatology* [*A.M.A. Arch. Derm.*] **78**, 490–499, Oct., 1958. 2 figs., 36 refs.

At the Albert Einstein Medical Center, Philadelphia, the authors attempted to analyse by biostatistical methods the results of topical application of steroids in the treatment of inflammatory dermatoses. The double-blind paired-comparison method was used in studying the effect of three different steroid lotions and a control lotion base on 510 patients with various eczematous lesions. A special punch-card system was utilized for recording the effects, which are analysed in a series of tables.

There was no statistical difference between the results obtained with a steroid lotion and those obtained with the control lotion in groups broken down according to age, sex, diagnosis, skin thickness, and the presence or absence of stratum corneum in the affected area. Simi-

larly, no statistical difference in effect could be demonstrated: (1) between 0·1% fludrocortisone lotion and a control lotion base in 177 patients; (2) between 0·1% fludrocortisone lotion and 1% hydrocortisone lotion in 217 patients; and (3) between 1% hydrocortisone lotion and 1% prednisolone lotion in 116 patients.

Commenting on the lack of evidence in this investigation of the superiority of steroid lotions over the control lotion, the authors draw attention to the difficulty of evaluating the effect of drugs in diseases in which psychosomatic factors may play a part. The presence in the series of a large number of anxious, self-centred, emotionally labile, and easily impressed "placebo reactors" may well have had a profound effect on the results. In addition, in an essentially unselected group of patients "the large number of dermatoses unaffected by steroids might have obscured the few which benefited". The emollient and possible antipruritic effect of the *iso*propyl alcohol base and the small amount of medicament used may also have influenced the results. It is concluded that while topical application of steroids was not found to be superior to application of a control base, the former have nevertheless been shown to be dramatically effective in certain cases and should therefore not be used indiscriminately. *Benjamin Schwartz*

640. **Treatment of Psoriasis with Folic Acid Antagonists**
W. F. EDMUNDSON and W. B. GUY. *A.M.A. Archives of Dermatology* [*A.M.A. Arch. Derm.*] **78**, 200–203, Aug., 1958. 3 refs.

Folic acid antagonists are known to inhibit proliferation of connective tissue, anomalous and undifferentiated cells, and epithelial cells. Moreover, clinical improvement in psoriasis following treatment with one of these antagonists (aminopterin) has already been reported. The present authors review the results obtained with both aminopterin and the closely related amethopterin in the treatment of cases of psoriasis seen in private practice in Pittsburgh, Pennsylvania.

Because of the inherent toxicity of the drugs the dosages were kept relatively low. A group of 32 patients (16 male and 16 female) were given two courses of aminopterin each of 0·5 mg. daily for 6 days with a 3-day interval between; 8 of these patients received an additional course totalling 4·5 mg. 3 weeks later and 6 received one or more adjuvant courses of aminopterin 3 months or more apart. Another group of 17 patients (13 male and 4 female) were given amethopterin in a dosage of 2·5 mg. daily to a total of 30 mg.; 5 of these received additional courses later. A further 13 patients were given an initial course of aminopterin and subsequent courses of amethopterin.

Follow-up periods varied widely and the results "proved difficult to express", but a comprehensive table shows that in 48 of the 62 patients treated there was more than 50% improvement over the observation period. No significant difference was observed between the results obtained with aminopterin and those obtained with amethopterin, nor did age, sex, duration of the disease, type of psoriasis, or the number of treatment courses bear any relationship to the therapeutic response. However, of the 13 patients who received both drugs, 11 maintained more than 50% improvement.

None of the patients treated with amethopterin reported toxic effects; one patient receiving aminopterin complained of a sore mouth and another of a delay in menstruation, but in neither of these was there any significant change in the haematological picture.

Adjuvant therapy consisting of injections of vitamin B_{12} (cyanocobalamin) or riboflavine was given during observation periods, and most patients used a mercury soap in a motor-oil mixture locally, but it was considered that this medication did not influence the course of the psoriasis. *Benjamin Schwartz*

641. **The Treatment of Vitiligo with Psoralen Derivatives**
M. LEVAI. *A.M.A. Archives of Dermatology* [*A.M.A. Arch. Derm.*] **78**, 597–606, Nov., 1958. 8 figs., 7 refs.

The author reports the results of the treatment, at the Christian Medical College Hospital, Vellore, South India, of 123 patients suffering from vitiligo with psoralen derivatives, the drugs used being "meladinine" (in tablets containing 10 mg. of 8-methoxypsoralen and 5 mg. of 8 *iso*myleneoxypsoralen), "oxsoralen" (tablets containing 10 mg. of 8-methoxypsoralen), and "meladinine" (in alcoholic solution containing 7·5 mg. of 8-methoxypsoralen and 2·5 mg. of 8-*iso*myleneoxypsoralen per ml.) by topical application. Oral medication only was given in 94 cases (starting with 2 tablets daily and increasing to 3 or 4 if there was no response in 2 to 3 months), 10 patients received local medication only (2 or 3 times weekly), while 19 received a combination of both types of treatment; in all cases the patients were subjected to graduated exposure to sunlight. Blistering was common, particularly in the topically treated cases, but could usually be controlled by more cautious exposure to sunlight. Anorexia, nausea, vomiting, and irritability occurred with oral medication, and one patient developed a mild hypertension. The response to treatment was assessed as "excellent" in 68 patients (55%), but only 13 (10%) were completely cured, while 7 (6%) showed no pigmentary response whatsoever.

From the results, which are tabulated according to the percentage of repigmentation, it is seen that a combination of oral and local psoralen was the most effective method, while oral treatment alone was more effective than local treatment alone. Lesions on the head and neck, excepting the lips, responded favourably to treatment, but those on the hands and feet tended to be resistant. The best results were obtained in children, in adults with disease of short duration, and in cases of multiple lesions. The author suggests that the psoralen derivatives stimulate melanogenesis by acting synergistically with sunlight, but that they probably have little influence on the primary defect causing vitiligo, and notes that new lesions may appear during therapy.

[The fact that only 10% of these patients were cured, the tendency to relapse when treatment was discontinued, and the high incidence of undesirable side-effects show that the method described still leaves much to be desired in the treatment of vitiligo.] *Benjamin Schwartz*

Paediatrics

NEONATAL DISORDERS AND PREMATURITY

642. **Thermoregulatory Changes in the Metabolic Rate of Full-term Newborn Infants.** (Thermoregulatorische Veränderungen des Energiestoffwechsels bei reifen Neugeborenen)
K. BRÜCK, M. BRÜCK, and H. LEMTIS. *Pflügers Archiv für die gesamte Physiologie des Menschen und der Tiere* [*Pflügers Arch. ges. Physiol.*] **267**, 382–391, 1958. 2 figs., 17 refs.

In previous investigations (*Pflügers Arch. ges. Physiol.*, 1957, **265**, 55 and 1958, **266**, 518; *Arch. Gynäk.*, 1958, **190**, 512) the authors established that the fall in body temperature of the newborn baby and its low temperature during the first few days of life are not due, as has been supposed, to its inability to prevent heat loss from the skin by vasoconstriction. It seemed therefore that the behaviour of the body temperature reflected lack of production rather than excessive loss of heat.

In order to test this theory 11 newborn, full-term infants were studied in a climatic chamber at the Women's Clinic of the University of Marburg to establish the effect of changes in environmental temperature on the metabolic rate and on blood flow in the skin of the heel and of the calf. It was shown that even in the first hour of life a reduction of the temperature of the chamber from 32°–35° C. to 23° C. caused the metabolic rate to rise by more than 100%. By the 7th to 9th day a similar reduction caused the rate to rise by an average of 173%. Expressed in absolute values this response of the metabolic rate is already similar in degree to that of the adult under similar conditions.

The authors conclude that thermoregulation in the newborn infant does not differ in principle from that in the adult. The differences are entirely quantitative, and are due to the infant's relatively larger surface area and thinner coat of subcutaneous fat causing greater heat loss per unit of body weight than in the adult. The initial fall in temperature is due to cooling during the process of birth, to the circulatory changes and onset of respiration, and to the strain of other processes of adaptation to extra-uterine life, the ability of the infant to compensate for the loss of heat by an increase in metabolic rate developing only gradually during the first week of life.

Marianna Clark

643. **Replacement Transfusion as a Means of Preventing Kernikterus of Prematurity**
V. M. CROSSE, P. G. WALLIS, and A. M. WALSH. *Archives of Disease in Childhood* [*Arch. Dis. Childh.*] **33**, 403–408, Oct., 1958. 3 figs., 6 refs.

Experience in the prevention of kernicterus in all premature infants seen at Sorrento Maternity Hospital, Birmingham, between July, 1955, and June, 1957, is reported. The serum bilirubin level was estimated daily in all infants showing definite clinical evidence of jaundice during the first 8 days of life, replacement transfusion being given to those in whom the level either reached 18 to 20 mg. per 100 ml. or was rising rapidly. Of 1,320 premature infants, 92 required replacement transfusion for hyperbilirubinaemia not due to haemolytic disease. More than one transfusion was required by 18 of the infants, and in 19 instances transfusion was not satisfactory. There were 2 deaths, one of which could not be attributed to either the transfusion or kernicterus. Of the 90 survivors, 83 were followed up to the age of one year and one infant to the age of 9 months. In 5 of these neurological signs of kernicterus developed, but the authors consider that this complication could have been prevented, and give their reasons for this view. They conclude that until some better method of preventing kernicterus due to prematurity becomes available, replacement transfusion appears to be the best form of therapy.

J. M. Smellie

644. **A Longitudinal Study of the Growth and Development of Prematurely and Maturely Born Children. I. Introduction. II. Physical Development**
C. M. DRILLIEN. *Archives of Disease in Childhood* [*Arch. Dis. Childh.*] **33**, 417–422 and 423–431, Oct., 1958. 3 figs., 19 refs.

In continuation of her previous investigation with Richmond (*Arch. Dis. Childh.*, 1956, **31**, 390; *Abstr. Wld Med.*, 1957, **21**, 289) the author presents, from the University of Edinburgh, the results of a further study, in this case based on physical measurements taken half-yearly between the ages of 6 months and 2 years in a series of 544 premature and full-term infants born in two Edinburgh maternity hospitals in the period 1953–5, the mature controls being selected by taking the next mature birth recorded on the hospital list after every alternate premature birth. The series included 110 pairs of twins and the surviving member of a further 10 pairs, a total of 225 such infants. The housing, social class (by occupation of the child's father), and maternal efficiency were also assessed, the last named being graded on the basis of general cleanliness, the advantage taken of welfare clinic facilities, the management of the infant's eating, sleeping, and toilet training, family relationships, and maternal health.

Throughout the 2-year period the infants' mean weights were closely related to the mean birth weight. In regard to height, those largest at birth maintained their height superiority at the end of the 2 years: the height increments were greatest where maternal efficiency was highest. In all the premature groups (boys, girls, singletons, or twins) there was a striking excess of maternal inefficiency, poor diet, and number of illnesses. By the application of the technique of intercorrelation and regression analysis it was shown that genetic and

environmental factors were of approximately equal importance in their effect on growth, whether measured by weight or height increment, at the age of 2 years.

R. S. Illingworth

CLINICAL PAEDIATRICS

645. Severe Infantile Hypercalcaemia with Special Reference to the Facies

M. C. Joseph and D. Parrott. *Archives of Disease in Childhood* [*Arch. Dis. Childh.*] **33**, 385–395, Oct., 1958. 16 figs., 40 refs.

The authors describe 4 cases of infantile hypercalcaemia seen in patients aged 4 months to 2 years at Guy's Hospital, London, with particular reference to the typical facies as observed in severe cases. This is usually that of an irritable child; the epicanthic folds are marked and often emphasized by the presence of a concomitant squint; the nose is pinched and *retroussé* so that the nostrils point forwards; the upper lip is prominent, appears loose, and lacks the usual bow, while the mouth is usually kept open, the lower lip hanging slackly; the chin recedes, but the brow is rounded and prominent in front of hollowed temples. Though the ears have been described as " low set ", the authors consider that this is an illusion caused by the backward tilting of the head, and it may be further emphasized by a short ramus to the mandible and a high vortex of the skull when these are present. (Photographs of 2 of the patients, to illustrate the facies, and diagrams of the facial characteristics accompany the paper.)

Of the 4 cases described, 3 showed the typical facies. All 3 presented with a history of vomiting and failure to thrive, with raised serum calcium and blood urea levels and an apical systolic murmur. Hypertension was present in 2 in whom the blood pressure was recorded. Two of these children were mentally retarded, while the third died of whooping-cough before the mental status could be assessed. Radiography revealed in all 3 increased density of the base of the skull, the periorbital bones, and the ends of the long bones, and in 2 cases of the borders of the vertebrae. The 4th case was milder in all respects and the facies was normal. The blood chemistry at first suggested an infantile renal acidosis, but later the serum calcium level rose, as did also that of the blood urea. Radiographs showed increased density of the skull, long bones, vertebrae, and pelvis. However, after treatment with cortisone recovery was almost complete at the age of 4 years 9 months, there being no mental retardation, although some increased density of the skull and periorbital bones persisted.

Calcium balance studies in the 3 severe cases showed excessive retention of dietary calcium. The administration of cortisone, though effective in lowering the serum calcium level, increased the percentage absorption. It is usually stated that there are two types of infantile hypercalcaemia—the first severe with typical facies, radiological changes, hypertension, failure to thrive, and severe mental retardation, and the second benign, there being only failure to thrive and a raised serum calcium level. The present authors suggest that this division is artificial and that mixed cases occur. It is true that the typical facies and radiological changes at the base of the skull are seen only in severe cases, but even the milder cases of the condition are not always " benign " since some of them end fatally.

H. G. Farquhar

646. Study of Fat Absorption Utilizing I^{131}-Labeled Corn Oil in Infants and Children With and Without Steatorrhea

S. Spector, W. Matthews, F. J. Lemm, Y. Van Erp, and J. Cline. *Pediatrics* [*Pediatrics*] **22**, 515–524, Sept., 1958. 3 figs., 9 refs.

The authors describe, from the Babies and Children's Hospital (University Hospitals of Cleveland, Ohio), a method of determining fat absorption in which corn oil labelled with radioactive iodine is used as the test meal, and then report the findings in 13 children with cystic fibrosis of the pancreas and 33 controls. In the children without steatorrhoea the degree of fat absorption depended on age; infants under 1 year absorbed an average of 78% of the fat, children aged 1 to 2 years an average of 90%, and those over 2 years an average of 97%. The average fat absorption in the 13 patients with steatorrhoea was 44% (range 23% to 66%). In 9 of 11 patients who were given a second test meal with added pancreatin the average fat absorption rose to 83%.

This method of estimating fat absorption appears to be accurate and to be more simple than the methods commonly used in performing fat balance studies.

Winston Turner

647. A Test for Coeliac Disease

W. W. Payne and V. Jenkinson. *Archives of Disease in Childhood* [*Arch. Dis. Childh.*] **33**, 413–416, Oct., 1958. 9 refs.

The gliadin tolerance test for wheat sensitivity in suspected coeliac disease, described by Weijers and van der Kamer (*Acta paediat.* (*Uppsala*), 1955, **44**, 536) was performed at the Hospital for Sick Children, Great Ormond Street, London, in 33 cases of coeliac disease and in a number of convalescent patients with diseases not involving the alimentary tract who served as a control group. It was shown that the mean maximum increment of the apparent plasma glutamine level was significantly greater in coeliac disease than in the controls. There was no relationship between age and magnitude of increase of apparent plasma glutamine level in the controls or the patients and no correlation between magnitude of rise of apparent glutamine level and the phase of the disease, whether symptoms were active or controlled by treatment. In 5 cases of coeliac disease tested first while taking a gluten-free diet and then a normal diet no relationship could be demonstrated between the type of diet and rise in the plasma glutamine level.

While these results confirm the observations of Weijers and van de Kamer, the increase in the plasma glutamine level in the present patients was not as great as in those of the Dutch workers. A very wide standard deviation was evident, and the authors conclude that this test in its present form is unreliable in individual cases. Nevertheless it is considered that further investigation of

the amino-acid content and peptide pattern of the blood after ingestion of gliadin or fractions of this protein should be encouraged. *J. M. Smellie*

648. **Saliva, Tears and Duodenal Contents in Cystic Fibrosis of the Pancreas**
P. A. DI SANT'AGNESE, H. GROSSMAN, R. C. DARLING, and C. R. DENNING. *Pediatrics* [*Pediatrics*] **22**, 507–514, Sept., 1958. 17 refs.

In this paper from Columbia University and the Babies Hospital, New York, the authors discuss some physical and chemical characteristics of parotid and mixed saliva, duodenal contents, and tears from patients with cystic fibrosis of the pancreas and from a comparable group of controls. The concentrations of chloride and sodium in mixed saliva and tears were significantly increased in the patients compared with the controls, but there was a wide overlap of the two groups which lessened the value of these findings for diagnostic purposes. In contradistinction to this, as the authors point out, there is a marked difference between the concentrations of these ions in the sweat of patients with cystic fibrosis of the pancreas and the concentrations in controls, with almost no overlap, and the sweat test has become a reliable procedure for differentiating cystic fibrosis from other conditions which it resembles. In the present investigation the concentrations of potassium were similar in both groups. The parotid secretion rate was significantly higher in the patients than in the controls, but the enzyme activity of saliva was similar in both. Wide variations in the proteolytic activity of the duodenal fluid were noted, but were not associated with changes in the fluid electrolyte levels in either group. The authors draw attention to three defects in secretion of exocrine glands in cystic disease of the pancreas—abnormality of mucus secretion, high electrolyte concentrations in sweat, tears, and saliva, and an increased rate of secretion of the parotid glands. *Winston Turner*

649. **Cystic Fibrosis of the Pancreas: Intestinal Absorption of Fat and Fatty Acid Labeled with I^{131}**
K. REEMTSMA, P. A. DI SANT'AGNESE, J. R. MALM, and H. G. BARKER. *Pediatrics* [*Pediatrics*] **22**, 525–532, Sept., 1958. 1 fig., 20 refs.

Fat absorption in cystic fibrosis of the pancreas was studied in 10 patients (aged 6 to 18 years) and 13 control children without gastro-intestinal disease at the Presbyterian and Babies Hospitals, New York. For this purpose a test meal of neutral fat labelled with radioactive iodine was given on one occasion and a meal of fatty acid similarly labelled was given on another, the serum content and urinary excretion of the isotope being determined at frequent intervals. In 8 patients with cystic fibrosis of the pancreas there was pancreatic achylia, while in 2 the duodenal tryptic activity was normal. In the 8 patients with deficient trypsin activity in the duodenal contents the intestinal absorption of neutral fat was much diminished, the absorption of fatty acid being reduced to a lesser extent. The 2 patients with normal trypsin activity in the duodenum appeared to absorb neutral fat better than the 8 with pancreatic achylia, but the values for fatty-acid absorption were similar in both groups. Fatty acid appeared to be absorbed more slowly in these patients than in the controls.

The authors consider that in the 8 patients with pancreatic achylia there was a double defect of absorption —namely, a deficiency of pancreatic digestion and also a non-pancreatic factor, probably a dysfunction of intestinal absorption. *Winston Turner*

650. **Congenital Absence of the Intrahepatic Bile Ducts**
L. HAAS and R. H. DOBBS. *Archives of Disease in Childhood* [*Arch. Dis. Childh.*] **33**, 396–402, Oct., 1958. 10 figs., 22 refs.

The authors describe 2 cases of congenital absence of the intrahepatic bile ducts seen at the London Hospital in female patients aged 2½ and 3 years respectively. Both patients developed jaundice, which appeared on the 2nd and 4th days of life respectively, and both had signs of an obstructive jaundice, bile being again present in the stools by the second month in one case, and by the eighth month at latest in the other. The jaundice became progressively less and investigations showed normal liver function, except for a raised serum bilirubin level of 4·5 mg. per 100 ml. in both cases and in one a serum alkaline-phosphatase level of 54 units. In both cases the serum cholesterol level was raised, being 1,200 and 1,600 mg. per 100 ml. respectively; in the second case the serum total lipid content was 3,800 mg. per 100 ml. and the serum lipoprotein content 1,300 mg. per 100 ml. Both children were stunted, and both developed pruritus followed by the appearance of xanthomata, in one case on the palms of the hands, soles of the feet, elbows, ankles, in the creases of the skin, and along the gum margins, and in the other in the skin flexures and on the buttocks. In both the liver and spleen were enlarged. One died aged 2 years 9 months of acute pyelonephritis, there being a terminal rise of the serum bilirubin level to 13·6 mg. per 100 ml.; the other is alive.

Histological examination of liver biopsy specimens showed in both children absence of bile ducts in the portal tracts, but normal intralobular canaliculi. The architecture of the liver was very little disturbed, there being only a slight increase of fibrous tissue in the portal tracts and a slight increase in cellularity. (Photomicrographs which demonstrate these changes well are reproduced, and are compared with the appearances of the liver in extrahepatic biliary atresia.) In the child who died patency of the extrahepatic ducts was confirmed and xanthomata were found in the endocardium, the subintima of the great vessels, and on the epiglottis. The authors analyse 8 other cases collected from the literature, in 2 of which the patients reached the ages of 10 and 12 years respectively. They suggest that the condition can be diagnosed in a child who has obstructive jaundice in the first week of life, in whom the jaundice becomes gradually less severe, and in whom the serum lipid level rises and xanthomata appear. The diagnosis is confirmed by the demonstration of the absence of bile ducts in the portal tracts by biopsy. The condition is a congenital malformation and treatment can therefore be only symptomatic. Methyltestosterone may relieve

the severe pruritus. In the 2 cases described no lowering of the serum lipid level or regression of the xanthomata was obtained by administration of a diet devoid of animal or saturated vegetable fats. *H. G. Farquhar*

651. **The Prevalence of Dental Caries in Relation to Maturity**
J. M. MANSBRIDGE. *Archives of Disease in Childhood* [*Arch. Dis. Childh.*] **33**, 455–464, Oct., 1958. 2 figs., 16 refs.

The author has investigated, at the University of Edinburgh, the dental state and physical maturity of 1,730 children aged 5 to 17 years who formed part of an anthropometric survey carried out by Provis and Ellis (*Arch. Dis. Childh.*, 1955, **30**, 328), so that other physical measurements were available. The usual "D.M.F." (decayed, missing, filled) index was used to measure the prevalence of caries in permanent teeth. The children were first ranked in order of height and then in order of weight for each age and sex separately, and also each yearly age group was divided into thirds for comparison of the greatest third with the least third for weight and height separately.

Up to 11 years of age there was no relation between caries and height or weight. Thereafter, the taller children had more D.M.F. teeth with the exception of the 17-year-old girls, among whom the shortest girls had the higher D.M.F. index. In regard to weight, the heaviest girls over 11 years of age had more D.M.F. teeth than the lightest, but of the boys, only those aged 14, 15, and 16 had the greater number, the other age groups showing less consistency. A clinical assessment of sexual maturity was available for all the children, based on growth of body hair, genitalia, age of onset of menstruation, and breast enlargement, three main groups being recognized, namely, non-pubescent, pubescent, and adolescent. However, owing to the different numbers of teeth erupted in the various groups it became obvious that only two comparisons could be made; these were between 31 pubescent and 35 adolescent girls aged 13, and between 28 pubescent and 28 adolescent boys aged 15. Since the amount of caries depends partly on the length of time a tooth has been erupted a second comparison was made between all adolescent and all pubescent children, the condition of the 2nd molar teeth being disregarded.

In each series the adolescent children showed a greater incidence of caries. Further statistical analysis was required, however, since the results might have been influenced by differences in the number of teeth erupted and the chronological age. Using the total number of 629 boys and 581 girls as a sample, and discounting the effects of these two factors, it became evident that among boys there was a highly significant increase in D.M.F. teeth with maturity, but no such phenomenon among the girls. The author points out that Widdowson has shown that the total sugar consumption of boys is far greater than that of girls, but this does not explain entirely the different results between the adolescent and the other groups in this study. He suggests that there is evidence that maturity also plays a part in the production of caries. *J. G. Jamieson*

652. **The Investigation and Significance of Persistent and Recurrent Urinary Infection in Children**
W. I. FORSYTHE and I. R. WALLACE. *British Journal of Urology* [*Brit. J. Urol.*] **30**, 297–302, Sept., 1958. 13 refs.

The significance of persistent and recurrent urinary infections in children was investigated in 51 patients (17 boys and 34 girls), aged one to 14 years, at the Royal Belfast Hospital for Sick Children and the Ulster Hospital for Children and Women, Belfast. The symptoms and full clinical examination did not, as a rule, disclose the cause, but abnormalities of the genito-urinary tract were discovered in 18 patients by intravenous pyelography and in another 26 by micturition cystography. Retrograde pyelography was required to establish the exact nature of the abnormality in 5 cases only. The authors consider that retrograde cystography is preferable to the intravenous method, and regard as abnormal a dilatation of the internal sphincter during micturition of more than 10 mm. Abnormal widening of the internal sphincter, allowing more ready access of bacteria from the perineum, was present in 9 girls. Vesico-ureteral reflux was found in 10 boys and 10 girls. In 5 of the boys it was due to obstruction at the bladder neck or in the posterior urethra; in the remaining 5 boys and in the girls the reflux was probably due to inflammatory weakening of the vesico-ureteral junction. There was abnormal widening of the internal sphincter in 5 girls with reflux. It is pointed out that weakness of the vesico-ureteral junction and internal sphincter may be congenital or the result of infection. Lesions causing obstruction or stasis were found in 11 of the 17 boys, whereas only one of the girls had an obstructive lesion (narrow meatus). Thus even if 5 girls with cord bladder due to spina bifida are included it would appear that obstructive lesions are uncommon in girls.

Charles Nicholas

653. **Education of Cerebral Palsied Children. The Role of Meprobamate: a Preliminary Evaluation**
B. E. KATZ. *Journal of Pediatrics* [*J. Pediat.*] **53**, 467–475, Oct., 1958. 11 refs.

Children with cerebral palsy have two major groups of symptoms which handicap their education: (1) purposeless body movement with spasticity; and (2) emotional difficulties leading to abnormal behaviour. Both these symptom complexes must be treated to allow full intellectual development. Meprobamate, a muscle relaxant capable of relieving anxiety and emotional tension, has been shown to lessen behaviour disturbances, and the present study was undertaken to assess the influence of the drug on learning ability.

Of 19 patients attending a school for children with cerebral palsy, 10 were selected for treatment and their progress compared with that of the remaining 9. The ages of the 10 treated patients ranged from 5 to 24 years and their I.Q. from normal to below 60 on the Terman–Binet Scale. The degree of physical handicap varied from mild to severe, and behaviour was mildly or moderately disturbed in 5 cases and normal in 5. One patient could not read and the other 5 had varying reading abilities. All were physically healthy, and all had

been under observation for at least 2 years. [Corresponding details in respect of the 9 untreated patients are not given.] Meprobamate was given once daily in a dose of 200 mg., increasing by 200 mg. at fortnightly intervals until a satisfactory response was obtained, treatment being discontinued during the holidays and at week-ends unless the parents asked for it to be continued, as they did in 6 cases.

A weekly assessment was made of: (1) degree of muscle relaxation; (2) magnitude of spastic or involuntary movement; (3) ease of handling; (4) outlook and attitude; (5) endurance; (6) attention span; (7) ability to learn. Evaluation of the first 3 was performed by the medical officer and physiotherapist and followed closely the standards defined by Gillette (*Int. Rec. Med.*, 1956, **169**, 453; *Abstr. Wld Med.*, 1956, **20**, 474) and of other authorities where applicable. The last 3 factors were evaluated by 2 teachers, and the patients' outlook and attitude by all 4 observers. Details of the response of each subject to various doses of the drug are tabulated.

The 9 patients not given meprobamate continued at the previous retarded rate, while those treated became more manageable both physically and emotionally during the 80 weeks of the study. They were less fatigued and more alert, while in 9 out of the 10 accelerated reading progress and ability to learn were observed, probably attributable to reduced spasm and better concentration, with increased attention span. The dosage of the drug had to be adjusted carefully to each child's specific requirement, the maximum level varying from 400 to 1,600 mg. daily.

While it is not claimed that the results prove that meprobamate has a direct effect on attention span or learning ability, they do show that the response to instruction of the children studied improved during the period of the study, and the author considers that meprobamate was responsible for this unexpected level of progress.

M. R. Medhurst

654. **Learning Disabilities Associated with Lesser Brain Damage**

H. E. Thelander, J. K. Phelps, and E. W. Kirk. *Journal of Pediatrics* [*J. Pediat.*] **53**, 405–409, Oct., 1958. 4 refs.

The authors have studied children with cerebral palsy and other evidence of brain damage over a period of 5 years at a special unit of the Children's Hospital of San Francisco. This consists of an admission clinic, a nursery school, a special evaluation service, and a follow-up clinic. The children are observed by both teachers and psychologists. In addition to the usual standardized intelligence tests and developmental scales, special tests are used to assess perception, visual–motor co-ordination, auditory memory span, and qualitative approach to tasks. These tests often have to be adapted to the child and are therefore not standardized, but an attempt is being made to correlate the results of various tests with known brain damage and particular patterns of behaviour.

Seven cases are quoted to illustrate how minimal motor disturbance may be accompanied by specific perceptual defects which lead to difficulty in learning. Ordinary neurological examination, electroencephalography, and air encephalography are too insensitive to detect such abnormalities and need to be supplemented by specially devised tests carried out by skilled personnel. The more subtle defects which lead to learning difficulties are those of: (1) expressive speech; (2) understanding of oral commands; (3) writing; (4) perception of hearing; (5) memory; (6) control of hyperactivity; and (7) emotional control.

Children with cerebral damage causing aberrations of this type, but with minimal motor involvement, merge with those who have no demonstrable motor handicap and thus tend to be excluded from the category of cerebral palsy. If their deficits are not understood and treated by an intensive rehabilitation programme serious emotional maladjustment may result.

M. R. Medhurst

655. **Progressive Cerebral Degenerations of Childhood**

H. Stevens and A. Dekaban. *Neurology* [*Neurology (Minneap.)*] **8**, 677–681, Sept., 1958. 9 figs.

Writing from the George Washington University School of Medicine, Washington, D.C., the authors discuss the syndrome of progressive cerebral degeneration in infants and describe 5 illustrative cases. These patients developed normally up to ages varying from 3 to 24 months, but then began to suffer from convulsions which were associated with arrest and later with retardation of development. The outlook in all was bad; in one case a diagnosis of cerebral lipidosis was established by brain biopsy, and in 2 fatal cases the post-mortem diagnoses were an infantile form of cerebellar ataxia and a metachromatic type of diffuse sclerosis respectively.

The authors consider that progressive cerebral degeneration is a clinical syndrome without a unitary pathological process. They urge that the older, resounding, but not informative eponyms for these diverse syndromes be abandoned and a reclassification attempted in the light of recent knowledge of genetics, histopathology, and biochemistry. In some cases this might permit appropriate genetic counsel to be offered to parents. The available investigations at present are (1) examination and analysis of the urine for evidence of galactosaemia, phenylpyruvic oligophrenia, cytomegalic inclusion disease, or metachromatic type of diffuse sclerosis; (2) radiography of the skull for evidence of cytomegalic inclusion disease and toxoplasmosis; (3) electroencephalography to detect hypsarrhythmia and other conditions; (4) pneumoencephalography to detect certain congenital malformations, such as hydrocephalus and cerebral atrophy; and finally (5) brain biopsy, which in the authors' view is not performed sufficiently often in cases of this type.

[The sweeping introduction on general lines to this paper is hardly substantiated by the presentation of 5 dissimilar case histories and the total absence of any reference to the literature on this subject, from which may be cited the paper by Illingworth (*Arch. Dis. Childh.*, 1955, **30**, 529; *Abstr. Wld Med.*, 1956, **20**, 68).]

John Lorber

Public Health and Industrial Medicine

656. **Increase of Tuberculosis Mortality in Elderly Men from 1940 to 1950**
M. A. MONK and M. TERRIS. *American Journal of Public Health* [*Amer. J. publ. Hlth*] **48**, 1020–1030, Aug., 1958. 7 figs., 12 refs.

The authors draw attention to the increase in mortality from tuberculosis among elderly men during the period 1940–50 which was observed in Upstate New York, many large cities of the U.S.A., England and Wales, many countries of Western Europe, Australia, New Zealand, and Hawaii. They examine possible reasons for this, and reject changes in classification, migration of negroes, accumulation of deferred deaths from tuberculosis, and the possibility of a high death rate in a cohort of men particularly susceptible to this disease. They consider that this rise (the death rate started to fall again in the 1950s) was a temporary one caused by certain war-time conditions, including a resumption or continuance of work by elderly men and nutritional deficiencies.
John Pemberton

657. **Medical Aspects of Adoption**
J. A. BLACK and F. H. STONE. *Lancet* [*Lancet*] **2**, 1272–1275, Dec. 13, 1958. 8 refs.

The authors of this paper from the Royal Hospital for Sick Children, Glasgow, discuss some of the medical problems of child adoption, and describe a few typical cases. The difficulty of assessing the mental and physical state of an infant is stressed. Frequently, details of delivery and the neonatal state are not available, and a family history, which is of particular importance, is often unobtainable. As a result, hereditary conditions such as acholuric jaundice and genetically determined diseases such as Friedreich's ataxia or gargoylism are not detected. The physical examination of the infant should include an estimate of the stage of neuromuscular coordination, a view of the optic disks, and some hearing tests. Renal disease and phenylpyruvic oligophrenia can be detected on examination of the urine. A cardiac murmur in the absence of other evidence of cardiac disease should not exclude a child from adoption. In one case cited a child with cerebral palsy was adopted as a normal infant at 5 weeks; knowledge of the birth history would have made the examiner suspect an intracranial lesion. Profound personality changes in older children may stem from lack of a continued affectionate relationship with the mother in very early life.

Subjects wishing to adopt a child should be examined to ensure that they have no communicable disease and are not likely to become incapacitated before the child is independent. They may be severely disturbed psychologically, thus creating difficulties for the child. The authors consider that expert opinion may be necessary to assess the applicants, and that it is reasonable to reject a couple whose capacity for normal human relationship is defective. It is suggested that the case committee should include a doctor who can assess the value of the medical evidence offered. If the birth history is suspect the applicants should be told the circumstances and warned that further examination is necessary. A child should not be placed with applicants before the age of 6 weeks, even with the consent of the mother, since a return to the mother following a change of mind on her part may prejudice the success of adoption of another child by the applicants.
J. G. Jamieson

IMMUNITY AND EPIDEMIOLOGY

658. **The Influence of Natural and Artificially Induced Immunity on Alimentary Infections with Polioviruses**
J. P. FOX, H. M. GELFAND, D. R. LEBLANC, and D. F. ROWAN. *American Journal of Public Health* [*Amer. J. Publ. Hlth*] **48**, 1181–1192, Sept., 1958. 8 refs.

In January, 1956, anti-poliomyelitis vaccination with 2 doses of Salk vaccine was given to all incompletely immune children in the 136 representative households in Louisiana which had been studied for the previous 30 months with the aim of establishing the circumstances in which naturally acquired subclinical primary immunizing infections with poliovirus occurred, as previously described (*Amer. J. Hyg.*, 1957, **65**, 344 and 367; *Abstr. Wld Med.*, 1957, **22**, 484 and 485). A third (booster) dose was given in January, 1957. After vaccination 117 of these families agreed to remain under modified observation, and the authors now present a preliminary report on the household episodes of poliomyelitis infection in these families up to August, 1957; they also further analyse the previously obtained material the object being to ascertain whether immunization with killed poliovirus creates an immune barrier to virus spread.

Between the inception of the study in 1953 and August, 1957, a total of 177 household episodes of infection with poliovirus were detected. The annual incidence varied, but the 47 episodes in 1956 actually represented a slightly greater relative incidence compared with that in the years preceding vaccination, whereas the fact that only 6 episodes occurred in 1957 (up to August) appeared to reflect a true reduction in incidence. The development of antibody induced by vaccination had been excellent in the children already possessing heterologous antibody to one or 2 types of the virus, but among those who were negative to all 3 types nearly one-quarter failed after the booster dose to develop antibody to Type-1 and one-half to Type-3 viruses. In individuals with naturally acquired homologous immunity living in the households in which cases of poliomyelitis occurred, measurable resistance to reinfection (and reduced duration of faecal excretion of virus when infection did occur) were observed, although vaccination apparently did little to reduce susceptibility; in contrast, among persons with-

out natural immunity, vaccination exerted no influence either on the duration and course of alimentary infection or on susceptibility. No significant correlation was observed between the antibody titre resulting solely from vaccination and the number of infections, but among persons with previous natural immunity the proportion of proved reinfections decreased significantly with an increase in preinfection titre of homologous antibody. Resistance did not differ significantly in relation to the 3 viral types.

The study also showed that infected vaccinated children " appeared to be just as effective sources for intrahousehold spread of virus as did unvaccinated children, whereas some evidence was obtained that infected but naturally immune children are ineffective sources ". In one episode in 1957 virus was being excreted in the stools of one of 2 vaccinated children for at least 3 months before the infection spread to another member of the family. This delay is considered to provide strong evidence against the spread of poliomyelitis infection being from a pharyngeal source. From these findings the authors conclude that the widespread use of Salk vaccine does not influence the dissemination of poliomyelitis virus and that the decline in episodes of infection observed in 1957 was not due to such vaccination. They suggest that the creation of an immunological barrier to spread of the virus will be achieved only when attenuated live-virus vaccine can be safely used. *A. Ackroyd*

659. **Vaccination against Poliomyelitis with Live Virus Vaccines. 4. A Review of the Present Position**

G. W. A. Dick and D. S. Dane. *British Medical Journal* [*Brit. med. J.*] **2**, 1184–1186, Nov. 15, 1958. 17 refs.

Compared with the formalinized type, vaccines containing living attenuated poliovirus, which are given by mouth, " give a broader type of immunity which will for a time prevent or modify subsequent infection of the alimentary tract with poliovirus ". Thus the use of live vaccines might interfere with the natural spread of the virus, which formalinized vaccine appears to be incapable of doing. In the present paper the authors review the progress which has been made in preparing such vaccines from strains of poliovirus selected for their comparative lack of neurotropism in the monkey and in testing them for effectiveness and for their safety both to the vaccinee and to the community.

All the vaccine viruses prepared in monkey kidney tissue culture which have so far been tested have shown some change towards greater neurotropism after growth in the human gut, though with one exception this has not been enough to cause anxiety for the safety of the vaccinee. Like the naturally occurring or " wild " strains, however, some of the vaccine viruses have shown a tendency to spread from those vaccinated to their contacts, and in the authors' opinion the viruses excreted by the vaccines in some recent trials cannot be differentiated from the less neurotropic strains of wild virus. The spread of such strains can do no harm provided that they are stable and cannot change to a more neurotropic form. Unfortunately, information on the stability of wild viruses is scanty and inconclusive, and the question whether the uncontrolled spread of poliomyelitis virus vaccine in the community is dangerous or beneficial can be answered only by means of field trials.

The authors suggest that in the absence of controlled field trials the effectiveness of live vaccines can best be judged by measuring the level of neutralizing antibody in vaccinated subjects. Trials of vaccine viruses grown in tissue culture have shown the response to be similar to that obtained with formalinized vaccine, with a similar decline in antibody level over the next year. Very high antibody levels may be attained after a third or booster injection of the formalinized vaccine, but it is doubtful whether feeding with live virus would have a similar effect in view of the resistance of the alimentary tract to re-infection with such viruses. On the other hand the development of this resistance raises the hope that persons so vaccinated would be similarly resistant to wild strains of the virus.

The authors discuss the possible use of attenuated poliovirus vaccines, which are cheaper to produce than formalinized vaccines, in countries in which the latter cannot be afforded. They emphasize the need, before such use, of careful trials during non-epidemic times and stress the difficulty of planning such trials. In view of the possibility of spread of the virus from vaccinees to contacts the aim of the trials should be to define the limits of safety of the vaccines as well as their effectiveness. *W. K. Dunscombe*

660. **Vaccination against Poliomyelitis with Live Virus Vaccines. 5. Neutralizing Antibody Levels One Year after Vaccination**

D. S. Dane, G. W. A. Dick, M. Briggs, and R. Nelson. *British Medical Journal* [*Brit. med. J.*] **2**, 1187–1188, Nov. 15, 1958. 5 refs.

This paper from the Queen's University, Belfast, reports investigations into the duration of the immunity induced by giving live attenuated poliomyelitis vaccines of Types 1 and 2 by mouth. In the first experiment 6 adult volunteers (5 male and 1 female) were given SM Type-1 virus and their serum tested for neutralizing antibody at frequent intervals immediately thereafter, the serum with the highest titre in each case being retested together with serum taken at least one year later. In all cases the prevaccination titre (expressed as the reciprocal) was less than 4. In 2 cases the titre rose to 179 and 359 respectively at 3 to 5 weeks, but in the remainder it never rose above 22 in the 9 weeks after vaccination. A year or more later the 2 subjects with previously high serum antibody levels still had fairly high titres (64 and 89 respectively); of the remainder, in 2 the titre had returned to the prevaccination level, but in one the titre had risen from 8 at 9 weeks to 256 at 15 months after vaccination. In this last case, however, it was found that between the 9th and 15th months after vaccination there had also been a marked rise in the level of antibodies to Type 2, suggesting that during this period he had had a natural poliovirus infection.

In the second investigation sera from 60 children vaccinated orally one year before with TN Type-2 poliovirus were tested and their content of neutralizing anti-

body compared with that of sera taken 2 months after vaccination. A number of these children were found to be excreting virus for at least 4 weeks after vaccination and reasons are given for believing that in some cases the virus continued to multiply in the gut even beyond this date. At the end of one year antibodies to Type 1 or 3 (presumably due to natural infections) had developed in 6 cases, and in these the rise in Type-2 antibody titre observed was regarded as partially due to heterotypic virus infections. Of 15 children who had not developed antibodies 2 months after vaccination, none had antibodies after one year, showing that the vaccination had not "taken". In the remainder the serum antibody level had undergone a marked fall comparable to that observed, after the injection of formalinized vaccine.

The authors conclude from their findings that there is no evidence that the immunity produced by living vaccines is any more durable than that given by the formalinized type. *W. K. Dunscombe*

661. **A Small-scale Trial of Type III Attenuated Living Poliovirus Vaccine**

S. K. R. Clarke, A. P. Goffe, C. H. Stuart-Harris, and E. G. Herzog. *British Medical Journal* [*Brit. med. J.*] **2**, 1188–1193, Nov. 15, 1958. 3 figs., 20 refs.

Investigations are reported from the University of Sheffield of which the main objects were to ascertain (*a*) whether in children previously immunized with Salk-type poliomyelitis vaccine the serum antibody level could be boosted by feeding with live attenuated virus; and (*b*) whether the virulence of the attenuated virus was increased by passage through the intestine. The 14 subjects were long-stay patients in an orthopaedic hospital and were 6 to 15 years old. All had previously received 2 injections of a British Salk-type vaccine and none was excreting virus. However, 6 had a high serum level of antibodies to Type-3 virus before the trial began, and 3 of these had antibodies (presumably naturally acquired) to Type 2 before vaccination.

All the children received one dose of Type-3 (Leon) virus, while 4 received a second dose. None showed any clinical signs or symptoms, but 5 excreted virus in the faeces for periods up to 30 days after vaccination, showing that in these cases multiplication of the virus in the intestine had taken place. Virus was not recovered from the faeces of 4 children who were fed virus twice.

Children who did not excrete virus showed no increase in the serum level of Type-3 antibody; of 5 who did excrete virus, 3 showed an increased level of Type-3 antibody, but no heterotypical increase, one showed no change, and in one the level actually decreased. The virulence of the viruses recovered was compared with that of the vaccine by intracerebral challenge in monkeys, virus isolation and histological examination being carried out on all animals developing paralysis. All the 5 strains recovered from the faeces showed increased virulence, and there was a suggestion that the degree of increase was related to the length of the period of excretion. All viruses recovered from the monkeys were of Type 3.

It was thus demonstrated that it is possible to infect the alimentary tract of children previously immunized with Salk-type vaccine with attenuated poliovirus in spite of the presence of antibodies in the blood. The authors suggest that age may be important in determining susceptibility to such infection, as 4 of the 5 infected children were among the youngest. The lack of uniformity of the antibody response, when it occurred, is emphasized, as also is the considerable increase in virulence of the excreted viruses. *W. K. Dunscombe*

662. **Evaluation of the Effectiveness of Anti-influenza Vaccination**

V. Pavilanis, A. Frappier, F. Somlo, A. Boudreault, and P. Claveau. *Canadian Medical Association Journal* [*Canad. med. Ass. J.*] **79**, 527–532, Oct. 1, 1958. 4 figs., 13 refs.

A polyvalent anti-influenza vaccine was made up by mixing monovalent vaccines of the following strains in the proportions stated: A/PR8/1934 (22·2%), A/FMI/1947 (22·2%), A/Cuppett/1950 (22·2%), and B/Lee/1940 (33·3%). An attempt was then made to assess the degree of protection afforded by this vaccine in four different groups of subjects—the inmates of a psychiatric hospital, civil servants of the City of Montreal, factory workers, and persons living in a semi-rural area. The total number of persons vaccinated amounted to 5,494, while 2,254 were injected with a non-virulent placebo liquid and 3,543 received no injection. Of the vaccinated persons, some received one and some two injections, and a third group received one injection and a second dose by inhalation of vaccine aerosol by the nasal route. The first dose was given in October or November, 1954, and the second, if any, in February, 1955. Vaccination [apparently by all the methods used] resulted in a considerable increase in the titre of antibodies against B/Lee/1940 and A/PR8/1934 strains and a weaker response to the other strains, the antibodies being assessed by the haemagglutination-inhibition method. The degree of antibody production was independent of the subject's age.

An epidemic of mild influenza due to a virus identical with the A/Cuppett/1950 strain occurred in the first three groups in March, 1955, the fourth group being unaffected. The degree of protection afforded by the vaccine varied in the three groups from 40% to 80%. At the same time it was noted that the incidence of influenza among subjects given the placebo injection, although higher than that in the vaccinated, was considerably less than among those given no injections. This is attributed to the fact that the subjects receiving placebo injections were drawn from the same wards or communities as those vaccinated and therefore benefited from the reduced incidence of infection among the latter. *Franz Heimann*

663. **Effect of Eradicating Brucellosis in Cattle on Incidence of Human Cases**

J. R. Held, H. Bauer, and R. L. West. *Public Health Reports* [*Pub. Hlth Rep.* (*Wash.*)] **73**, 1096–1100, Dec., 1958. 4 figs.

664. **A Study of Illness in a Group of Cleveland Families. XVI. The Epidemiology of Influenza, 1948–1953**
W. S. JORDAN, G. F. BADGER, and J. H. DINGLE. *American Journal of Hygiene* [*Amer. J. Hyg.*] **68**, 169–189, Sept., 1958. 7 figs., 19 refs.

The observations here reported from the Western Reserve University School of Medicine and the University Hospitals, Cleveland, Ohio, were made in the course of a study of the occurrence of illness in a group of 60 families, totalling 308 persons, who were kept under continuous supervision from 1947 to 1957. Influenza due to both A-prime (A′) and B strains of virus was found to occur throughout the 6-year period 1948–53, both in epidemics and as an endemic infection. The presence of the latter was indicated by a significant increase in the titre of A and B antibodies, as measured in the spring and autumn in successive years, in the blood of 5 to 10% of individuals, although they had had no recognized clinical signs or symptoms of the disease. [Similar evidence of the occurrence of asymptomatic infections with the influenza virus in non-epidemic periods has been found in Great Britain.]

Epidemics of influenza A′ occurred in 1950, 1951, and 1953 and of influenza B in 1952. During the former epidemics viruses were isolated from throat swabs or washings from 7 to 12% of the individuals and from 25% of the families. In 1950 the serological attack rate was 15% and in 1951 and 1953 it was 25%—roughly double the clinical attack rate. The families harbouring the virus in the 1950 epidemic seemed to be relatively spared in 1951, but such a difference was not apparent between the 1951 and 1953 epidemics. The data are consistent with the assumption that natural infection is followed by partial immunity for 2 years. The median serum levels of antibodies to different antigens were found to vary with age. Antibodies to the PR8 and Lee strains (which were prevalent up to about 1943 when they were replaced by the FM1 strains) increased in titre as a result of infection with the more recent A and B strains only in adults and older children, the younger children having presumably not been exposed to the earlier antigens.

Epidemics followed periods during which the antibody titre of the population as a whole was declining and were also associated with the emergence of minor antigenic variants. Recrudescences of influenza A seem to be determined chiefly by these two factors, together with the chance occurrence of such favourable circumstances as the aggregation of susceptible individuals.

H. Stanley Banks

665. **A Study of Illness in a Group of Cleveland Families. XVII. The Occurrence of Asian Influenza**
W. S. JORDAN, F. W. DENNY, G. F. BADGER, C. CURTISS, J. H. DINGLE, R. OSEASOHN, and D. A. STEVENS. *American Journal of Hygiene* [*Amer. J. Hyg.*] **68**, 190–212, Sept., 1958. 6 figs., 21 refs.

An important factor in the causation of recurrent epidemics and pandemics of influenza is the antigenic instability of the virus. Four families or sets of major variants of influenza virus A have so far been recognized: (1) the swine type, which was probably responsible for the pandemic of 1918–19; (2) the PR8 set, which were the first strains of influenza virus to be isolated from man in 1933 and were prevalent for the next 10 years; (3) the A-prime (A′) variants of the FM1 set, which then completely replaced the earlier strains and were responsible during the next decade for relatively minor epidemics in different parts of the world; and (4) the Asian type of 1957, characterized by a marked antigenic difference from previous types and by rapid, world-wide extension. Within 3 years after the emergence of the A′ viruses the median level of A′ antibodies in the blood of members of the 60 families under observation by the authors [see Abstract 664] was higher than that of antibodies to the earlier PR8 viruses. But when the epidemic of Asian influenza started in September, 1957, few, if any, members of this population had any specific immunity.

During the epidemic the virus was isolated from 126 (41%) of the 308 members, drawn from 52 (86·7%) of the families. The serological attack rate in unvaccinated persons was 55%, this figure being 2 to 3 times higher than that found in the 1950, 1951, and 1953 epidemics of influenza A′. The clinical attack rate was 23%. Although in artificial infections with the Asian virus the incubation period is stated to be 1 to 2 days, it was longer than 5 days in as many as 53% of cases in which successive cases occurred in the same family; no explanation for this difference has been found. The main incidence of the disease was in September and October, with a marked decline in November, this being the reverse of the usual pattern of seasonal incidence of acute respiratory disease. However, the total number of acute respiratory illnesses occurring in the population during these 3 months was not greater than the average for previous years. Thus Asian influenza apparently displaced, masked, or interfered with the other acute respiratory infections that might otherwise have occurred, so that the usual high wave of respiratory illnesses in November was not seen.

It was noted that for measuring antibody response the haemagglutination-inhibition test was more sensitive than the complement-fixation test. Vaccination with Asian-strain vaccine was carried out on 110 persons, but in many cases influenza supervened before the second dose could be given or less than 7 days after it. The incidence of influenza among the remainder was 52% less than expected, but the numbers were too small for this finding to be regarded as significant. *H. Stanley Banks*

666. **Staphylococcal Infection in a Maternity Hospital. Epidemiology and Control**
W. A. GILLESPIE, K. SIMPSON, and R. C. TOZER. *Lancet* [*Lancet*] **2**, 1075–1080, Nov. 22, 1958. 2 figs., 26 refs.

An investigation of the sources and mode of spread of staphylococcal cross-infection among full-term infants, carried out at the Bristol Maternity Hospital over a period of more than 2½ years, showed that most infants became staphylococcal carriers before they were 2 days old; the sequence of sites of colonization with *Staphylococcus aureus* was usually the umbilicus first, followed almost at once by the groin, and later the nose and the neck. Staphylococci spread more often from the

umbilicus to the nose than in the contrary direction. Infants who became heavy carriers of staphylococci in both the nose and umbilicus by the 2nd day of life later developed sepsis more often than other infants. Nasal carriage usually persisted until the infant's discharge from hospital.

The majority (69%) of the strains of staphylococci isolated were resistant to penicillin, and 18% of these were also insensitive to streptomycin and 14% to sulphonamide. Most of the staphylococci isolated belonged to Phage-groups I and III; those of Phage-group I, including Types 52A/79 and 80, both of which caused more sepsis than other strains of this group, were mostly isolated from the nose, while those of Phage-group III, which caused less sepsis, were more numerous in cultures from the umbilicus. Suggested methods of reducing cross-infection include the application of dusting powder containing hexachlorophane to the umbilicus and surrounding skin, including the groin, perineum, and axillae, and the use of chlorhexidine (" hibitane ") hand-cream by members of the nursery staff. The disinfection of blankets and garments resulted in no reduction of cross-infection. *Franz Heimann*

667. **A Staphylococcus Type-80 Epidemic in a Maternity Hospital. Illustrating Some Special Features**
M. C. Timbury, T. S. Wilson, J. G. P. Hutchison, and A. D. T. Govan. *Lancet* [*Lancet*] **2**, 1081–1084, Nov. 22, 1958. 11 refs.

Writing from the University of Glasgow, the authors describe an outbreak of staphylococcal infection resulting in 8 deaths which occurred in the sick nursery of a maternity hospital and was due to the sudden appearance of *Staphylococcus aureus*, Phage-type 80. The epidemic was characterized by an unusually high incidence of serious infections among the babies. Before the outbreak of the epidemic Type 80 had not been present in the hospital. During the epidemic period the incidence of all staphylococcal infections among the babies was 11%, of which the proportion due to Type 80 amounted to 8%. While nasal swabs of the medical, nursing, and auxiliary staff as well as tests of the environment of wards and nurseries showed a very low rate of isolation of Type 80, some of the other strains of staphylococcus were isolated from various sites in the hospital and also from the nose of many nurses. The hospital was temporarily closed and thoroughly disinfected. On its re-opening after 18 days it was no longer possible to isolate Type 80.

Investigations carried out after one month on 18 infants at home after discharge from hospital showed that 17 (94%) were staphylococcal nasal carriers, 4 carrying Type 80; after 4 months the corresponding figures were 7 (44%) and 2 respectively. Another interesting fact was that Type 80 did not show the same predominance in infections at home as in the hospital, and showed no tendency to persist unduly in the noses of the infected infants.

Various aspects of staphylococcal infection in young infants are discussed and some recommendations made. *Franz Heimann*

INDUSTRIAL MEDICINE

668. **The Use of Ultrasonics and High Frequency Currents for Removing the Carcinogenic Properties of Shale Tar.** (Применение ультразвука и токов высокой частоты для обезвреживания канцерогенной сланцевой камерной смолы)
O. L. Daneckaja. *Гигиена и Санитария* [*Gig. i Sanit.*] **23**, 29–35, No. 9, Sept., 1958. 6 figs., 9 refs.

The use of shale tar on an increasing scale in industry has been accompanied by a corresponding rise in the incidence of carcinoma of the skin among the workers concerned. Various methods of dealing with this problem have been suggested, and in this paper the results are given of an investigation into the use of ultrasonic radiation for reducing the carcinogenic properties of shale tar. In experiments on mice this tar was painted 3 times a week for 6 weeks on the skin after exposure of different batches of the tar to ultrasonic radiation of various frequencies and for various lengths of time.

It was found that the mice treated with non-irradiated tar developed squamous-cell carcinoma of the skin in a higher proportion than the others. The tar showing the greatest reduction in carcinogenic properties was that exposed to ultrasonic radiation at a frequency of 65·7 million cycles per second, exposure 1 hour 30 minutes, interelectrode distance 38 mm., mice treated with this batch showing a reduction of 95% in the incidence of carcinoma; with the tar treated with ultrasonic radiation at a frequency of 600,000 cycles per second, exposure 16 hours, thickness of layer of tar treated 15 mm., there was a reduction in incidence of 73%. The author points out that these methods can be used in practice at shale-gas plants.

[No suggestion is made concerning the possible mode of action of these forms of radiation.] *Basil Haigh*

669. **The Genesis of Tumours of the Bladder and Other Tissues with Special Reference to the Industrial Amines**
G. M. Bonser, D. B. Clayson, J. W. Jull, and L. N. Pyrah. *Proceedings of the Royal Society of Medicine* [*Proc. roy. Soc. Med.*] **51**, 965–970, Nov., 1958. 3 figs., 22 refs.

Experiments in dogs have shown that bladder tumours can be induced by administration of 2-naphthylamine, though in other species, particularly cats, attempts to induce these tumours have been less successful. In this paper from the University of Leeds the authors report the results of investigations carried out to determine whether the tumour-inducing factor is the amine itself or its metabolite 2-amino-1-naphthol. Estimation of the urinary excretion of 2-amino-1-naphthol after a test dose of 2-naphthylamine in several species showed that there appeared to be a parallel between the proportion of the dose excreted in the form of conjugates of 2-amino-1-naphthol and the biological potency of 2-naphthylamine, the proportion being higher in the dog than in any other animal tested. In the dog 2-amino-1-naphthol and its conjugates were detectable in the plasma, and the urine: plasma ratio was about 200:1, this high concentration of the suspected carcinogen by the kidney possibly

explaining the localization of the tumours in the urinary tract. Moreover, when pellets containing 2-amino-1-naphthol hydrochloride were implanted into the bladder in mice the incidence of tumours was considerably higher than when the amine itself was implanted.

The typical carcinogenic aromatic amines have one structural feature in common—namely, that the position *para* to the amino group is blocked by a large substituent. Thus they are likely to be more readily hydroxylated in the *ortho* than in the *para* position in the course of metabolism, and the present authors have found that the *ortho*hydroxyamines are in fact present in small amounts in the urine of animals which develop cancer of the bladder on administration of the aromatic amines. In their view this suggests that any compound which might produce *ortho*hydroxyamines in the body should be suspected of being carcinogenic, the site of the tumour depending on where the concentration of these metabolites is highest. Among such compounds are the *ortho*nitro- and *ortho*nitroso-phenols and the *ortho*-hydroxyazo compounds, the last named being of importance since they are being increasingly used to colour foods. The widespread impression that water-soluble compounds are harmless appears to be unsupported—indeed there is some slight evidence that at least one water-soluble compound—trypan blue—is a carcinogen.

Discussing these findings in relation to the problem of spontaneous bladder tumours in man, the authors suggest that *ortho*hydroxyamines may arise in the body as the result of normal or abnormal metabolism, and that human contact with compounds which the body is able to convert to *ortho*hydroxyamines should be avoided.

Ethel Browning

670. **A Statistical Study of Coal-mining Accidents**
F. D. K. Liddell and J. May. *British Journal of Industrial Medicine* [*Brit. J. industr. Med.*] **15**, 262–269, Oct., 1958. 1 fig., 4 refs.

The work here reported is based on a study of 3 bodies of data: (A) basic information about each compensable casualty occurring at the 900-odd collieries in Great Britain during the 5 years 1945–49; (B) more detailed information about compensable casualties occurring at 14 collieries during 1953; and (C) the compensable casualty rates at each colliery for 1953 and 1954, together with a variety of descriptive information about the colliery. The casualties studied included, at the extremes, fatalities and minor injuries, but excluded injuries which did not cause at least 4 days' absence from work.

Marked variations were revealed in habits of reporting and standards of recording, as a result of which the authors conclude that the compensable casualty rate does not appear to be a true reflexion of the degree of safety in collieries. Moreover, much of the background information essential for a detailed analysis was not available. The conclusions reached were therefore mainly negative although certain positive conclusions were drawn from Data A, and these were usually confirmed by Data B. The authors consider that the method of routine recording of accidents at collieries should be studied to ascertain whether it can be adapted to provide material more suitable for the purposes of research.

Analysis of the data showed that the incidence of serious accidents did not depend on age, but that the younger men had more of the less serious injuries than their elders. Men under 21 who had been seriously injured took much longer to return to work than those aged 21 to 30. The casualty rates were invariably highest among coalface workers, next highest among workers elsewhere underground, and lowest among surface workers. On the other hand absences were shortest among coalface workers because they sustained a high proportion of slight injuries, and this tended to obscure the fact that coalface workers also had about twice as many serious accidents as other workers. There did not appear to be any substantial differences in accident experience between particular occupational groups in the main places of work. The underground accident rate did not appear to increase with the size of the colliery, but in those where coal-raising was by drift, which were predominantly small, the rates were lower than in those of similar size in which coal was raised by shaft. Collieries with a high underground accident rate tended to have a high surface rate and vice versa, the rates in each colliery remaining relatively stable from one year to another.

R. G. Meyer

671. **Clinical Features of Chronic Dichlorethane Poisoning.** (Клиника хронической интоксикации дихлорэтаном)
N. A. Govorova and M. N. Sadčikova. *Гигиена Труда и Профессиональные Заболевания* [*Gig. Truda prof. Zabolev.*] **2**, 45–48, No. 4, July–Aug. [received Nov.], 1958. 8 refs.

Dichlorethane is widely used in industry, and the possibility of poisoning by inhalation of the vapour may arise. The literature is sparse and deals mainly with animal studies. The authors therefore have carried out an extensive investigation among workers handling this compound, usually in concentrations below the maximum permitted. Evidence of toxic effects was found in 30% of those examined.

A more detailed investigation was made of 24 persons who had worked in contact with dichlorethane for periods of 1 to 10 years and were suffering from chronic poisoning, slight in 7 cases but of moderate severity in 17; (no severe cases of poisoning by inhalation were seen). Typical symptoms were: headache, dizziness, drowsiness, general weakness, precordial pain, dyspnoea, and in some cases nausea. In the majority of patients the conjunctival, corneal, and pharyngeal reflexes were weak or absent. Vegetative changes of various types were occasionally observed, such as sweating, bradycardia, and loss of pain sensation. The blood pressure was low and the electrocardiogram showed diffuse myocardial changes; the liver was enlarged and tender; the amount of total and free acid in the gastric juice was diminished; and liver function tests showed impairment of the detoxicating and other functions of this organ. The authors state that in the early stages these changes are reversible, although liver function is slower to return to normal than the other features. More prolonged exposure, however, leads to the development of irreversible changes.

Basil Haigh

Forensic Medicine and Toxicology

672. **Effect of Small Doses of Alcohol on a Skill Resembling Driving**
G. C. DREW, W. P. COLQUHOUN, and H. A. LONG. *British Medical Journal* [*Brit. med. J.*] **2**, 993–999, Oct. 25, 1958. 6 figs., 32 refs.

In spite of an extensive literature there is very little precise information about the effects of alcohol on physiology or behaviour. Much of the information is contradictory, particularly concerning the effects of small doses. The objects of the investigation herein reported from the University of Bristol were to determine the effects of small doses of alcohol on performance on an apparatus known as the " Miles motor driving trainer ", to correlate the findings with the blood alcohol level and temperamental differences, and to study the accuracy of blood alcohol levels as estimated by measuring the alcohol level in urine and breath. The subjects were 40 volunteers aged 23 to 58 years (mean 31 years), most of whom took alcohol only occasionally. They were given a placebo and 4 different doses of alcohol designed to produce peak blood concentrations of approximately 20, 40, 60, and 80 mg. per 100 ml. To minimize the effects of practice a latin square design was used, each square containing 5 subjects and 5 doses, the square being repeated eight times with different subjects.

The peak concentration of alcohol in the breath followed the blood alcohol level in time, but the peak alcohol concentration in the urine occurred later and was higher than that in the blood. The ratio of urine alcohol to blood alcohol level was 1·252:1. Of the 3 instruments used to analyse alcohol in breath the " breathalyser " was the most satisfactory. Performance on the driving trainer deteriorated 16% with a blood alcohol concentration of about 80 mg. per 100 ml., mainly manifested by faulty positioning on the road. Marked individual differences in speed occurred, and there was a significant reduction in consistency of steering-wheel movements after alcohol. The response to alcohol was unrelated to age, sex, driving experience, or drinking habits of the subject. Extraverts were less consistent in control movements than introverts, but showed large increases in error; the mean error score of introverts was significantly less than that of extraverts.

Norval Taylor

673. **Carbon Dioxide Poisoning. Report of Eight Cases, with Two Deaths**
H. I. WILLIAMS. *British Medical Journal* [*Brit. med. J.*] **2**, 1012–1014, Oct. 25, 1958. 7 refs.

From the Institute for Medical Research, Penang, 8 cases of carbon dioxide poisoning occurring in the hold of a ship are reported, the particular hold having been loaded with onions 6 days before. Of 4 men who entered the hold first, all collapsed and 2 died; 4 others entered the hold for short periods and were only slightly affected. One of those who collapsed was a doctor, who had been unconscious in the hold for about 5 minutes before being extricated; the remaining 3 had been unconscious for up to 15 minutes. The clinical signs in the men who collapsed were coma, sterterous breathing, non-reactive pupils, conjunctival injection, tachycardia, and convulsions. There was no cyanosis in those who recovered, but post-mortem examination (external only) in the 2 fatal cases showed cyanosis of finger and toe-nail beds and buccal mucosa, with marked injection of the conjunctivae. Symptoms noted on entering the hold were difficulty in breathing, pungent smell, giddiness, pains in the joints and legs, and pain and dryness of the throat; consciousness was lost very rapidly. An accurate estimate of the carbon dioxide concentration in the hold was not possible, but it seems likely that it was of the order of 25 to 30%.

Norval Taylor

674. **Experiences in the Specific Treatment of a Case of Poisoning with E605 [Parathion] with Atropine and the Esterase Reactivator PAM.** (Erfahrungen bei der spezifischen Behandlung einer E605-Vergiftung mit Atropin und dem Esterasereaktivator PAM)
W. D. ERDMANN, F. SAKAI, and F. SCHELER. *Deutsche medizinische Wochenschrift* [*Dtsch. med. Wschr.*] **83**, 1359–1362, Aug. 8, 1958. 1 fig., 12 refs.

From the University Medical Clinic, Göttingen, the authors describe the case of a 29-year-old man who, while being taken to prison, attempted to commit suicide by drinking about 12 ml. of a solution of the organic phosphorus insecticide " E 605 " [parathion]. Immediately after swallowing the fluid he showed no signs of poisoning, but within a few minutes he vomited, collapsed, and lost consciousness, showing respiratory depression, cyanosis, and convulsions. Atropine to a total of 14 mg. was injected intravenously in 2-mg. doses over 15 minutes, each dose causing transient improvement in the breathing and cyanosis. As the respiration remained unsatisfactory, however, intubation of the trachea was carried out. Radiography showed a dilated heart and increased vascular markings in the chest. A further injection of 2 mg. of atropine restored the pupils to their normal size and caused a tachycardia of 120 per minute. The general condition remained unchanged, however, being marked by audible tracheal bubbling, superficial irregular breathing, and severe cyanosis.

At this juncture 50 ml. of a 1% solution of PAM (pyridine-2-aldoxime methiodide) was injected intravenously and caused a definite improvement within 10 minutes, the muscular twitching disappearing completely and the breathing becoming deep and regular. Consciousness was recovered and the patient responded to questions. To counteract further absorption of parathion from the intestinal tract a further dose of 0·5 g. of PAM was given intravenously. The blood pressure remained at 105/70 mm. Hg before and after the injection. The patient appeared normal, vomited the tube, and was

able to drink. The following morning he was still sleepy and somewhat cyanosed, and complained of weakness in both legs. There was a trace of albumin and a positive reaction for sugar in the urine, but the blood picture was normal. A further 1 mg. of atropine injected intramuscularly was followed by further improvement, the patient appearing calm and mentally clear. He made an uninterrupted recovery. He had ingested about 10 to 20 times the fatal dose of parathion.

Norval Taylor

675. **Successful Treatment of Quinidine and Procaine Amide Intoxication. Report of Three Cases**
F. WASSERMAN, L. BRODSKY, M. M. DICK, J. H. KATHE, and P. L. RODENSKY. *New England Journal of Medicine* [*New Engl. J. Med.*] **259**, 797–802, Oct. 23, 1958. 17 refs.

The effect of administration of molar sodium lactate on the toxic manifestations of quinidine and procainamide in 3 cases of atrial fibrillation and tachycardia is described in this paper from the Veterans Administration Hospital, Coral Gables, Florida. One patient had received 3 g. of quinidine sulphate in 20 hours, the second 1·8 g. of quinidine sulphate in 24 hours, while the third had been given 600 mg. of procainamide intravenously. Severe bradycardia with a fall in blood pressure developed in all 3 patients. In 2, the plasma quinidine levels were respectively 5·1 and 6·3 mg. per litre. Molar sodium lactate was given by intravenous infusion, 2 patients receiving 40 ml. each and one 250 ml. In all 3 cases there was immediate improvement with a rise in blood pressure and relief of the bradycardia, although 2 of the patients died 4 and 6 days respectively after treatment with molar sodium lactate. *V. J. Woolley*

676. **Organic Compounds of Cobalt in the Treatment of Cyanide Poisoning.** (Les composés organiques du cobalt dans le traitement de l'intoxication cyanhydrique)
G. PAULET. *Presse médicale* [*Presse méd.*] **66**, 1435–1437, Sept. 20, 1958. 2 figs., 13 refs.

The author points out that while it has long been known that cobalt can antagonize the effects of cyanide, the mineral salts of cobalt have proved to be too toxic to be used in this way. He has therefore observed the effects of cobalt gluconate and of ethylenediaminetetraacetate (EDTA) monocobalt and EDTA dicobalt in experimental studies of sodium cyanide poisoning in anaesthetized dogs.

He has shown that all three compounds restored the respiration and blood pressure of the dog to normal when given after the injection of sodium cyanide, and even when they were given at the same time as an infusion of sodium cyanide the appearance of the signs of cyanide poisoning was prevented. EDTA dicobalt was particularly effective: thus the intravenous infusion of 1 mg. of this compound per kg. body weight per minute protected the animal against the administration of 0·1 mg. of cyanide per kg. per minute by the same route. The author discusses the possibility of making use of these findings in the treatment of cyanide poisoning in man. In the mouse the intravenous LD_{50} dose of cobalt chloride is 25 mg. per kg. body weight, that of cobalt gluconate 32 mg. per kg., that of EDTA dicobalt 37 mg. per kg., and that of EDTA monocobalt over 200 mg. per kg. Discussing the mode of action of EDTA dicobalt, the antidote of choice, the author suggests that after its injection one cobalt ion is liberated and combines immediately with the cyanide, thus accounting for the immediate antidotal effect, while the remaining dicobalt ions combine more slowly with the cyanide. The compound formed in this way is not metabolized and is excreted in the urine. There has been as yet no clinical experience with this compound. *H. B. Stoner*

677. **Neuromuscular Block and Respirator Treatment in the Management of Severe Salicylate Intoxications.** [In English]
O. CELANDER and G. HAGLUND. *Acta anaesthesiologica Scandinavica* [*Acta anaesth. scand.*] **2**, 123–131, 1958. 12 refs.

Salicylate intoxication is more often the result of therapeutic administration than of accident, the incidence being highest in children under 6 years of age. The authors of this paper from the Children's Hospital, Gothenburg, Sweden, consider that it may often be overlooked, thus accounting for the relatively few deaths recorded. The main pharmacological properties of salicylates are rapid absorption from the proximal part of the gastro-intestinal tract and excretion by the renal tubules which is increased by an alkaline and decreased by an acid urine; hence in pyrexia and dehydration a cumulative effect may occur. The symptoms of varying degrees of salicylate intoxication are: (1) headache, vertigo, tinnitus, and deafness (mild); (2) confusion, sweating, thirst, and, in children, nausea and vomiting (marked); (3) delirium, convulsions, and hyperthermia (severe); and (4) stupor, coma, and collapse (grave). Hyperventilation, which is the chief symptom, arises from central stimulation, both direct and through chemoreceptors, and is not paralleled by an increase in oxygen consumption or carbon dioxide production. Tachypnoea occurs in addition. The authors emphasize that electrolytic imbalance eventually leads to metabolic acidosis and must be corrected. Hyperventilation should, in doubtful cases, prompt examination of the urine for the presence of salicylates. Quantitative blood analyses have not proved of any value in assessing the severity of the intoxication. In the authors' experience the pronounced hyperventilation may change to failure of respiration without any previous clinical warning, thus emphasizing the need for continuous careful observation of patients with salicylate intoxication.

Treatment consists in an immediate and liberal supply of fluids and calories, dextrose solution being given intravenously. Hyperthermia should be controlled and sedatives withheld. Exchange transfusion has not proved helpful. In respiratory failure treatment is by controlled respiration combined with neuromuscular block; D-tubocurarine is used as the blocking agent, tracheotomy is performed, and respiration maintained for about 2 days with a Gothia respirator. [The authors have done a service in providing this reminder of the widespread uses and dangers of salicylates.] *Michael Kerr*

Anaesthetics

678. **The Reaction to the Test Dose of D-Tubocurarine before Anaesthesia in Myasthenic and Hypersensitive Patients.** [In English]
P. HALL. *Acta anaesthesiologica Scandinavica* [*Acta anaesth. scand.*] **2**, 117–122, 1958. 14 refs.

The effect of the 5 mg. test dose of D-tubocurarine in 2 cases of unsuspected myasthenia gravis and one of hypersensitivity to the drug is described. It was striking, but easily managed by ordinary anaesthetic technique, and recovery was not unduly delayed. A simple clinical sign, inability to lift the head in the supine position, which is diagnostic of residual curarisation, is described, and it is suggested that it might be of value for screening out myasthenics on the anaesthetic room table.—[Author's summary.]

679. **Pre-anaesthetic Medication with Chlorpromazine. A Comparison with Morphine.** [In English]
V. DYRBERG and S. H. JOHANSEN. *Acta anaesthesiologica Scandinavica* [*Acta anaesth. scand.*] **2**, 133–147, 1958. 4 figs., 29 refs.

The effects of pre-anaesthetic medication with chlorpromazine and morphine in 323 women undergoing total abdominal hysterectomy under a strictly standardized anaesthesia are compared. Data indicating a high degree of comparability of the 2 groups of patients compared are given. The following observations provided the basis for comparison: (1) Degree of sedation: practically identical results were obtained from both drugs. (2) Reflex movements during the operation: no significant difference could be demonstrated. (3) Sweating during the operation: chlorpromazine-treated patients significantly less than morphine-treated patients. (4) Amount of succinylcholine used: differences of statistical significance between the 2 groups were not found. (5) Residual neuromuscular blockade in terms of immediate postoperative respiratory insufficiency and weakness of neck muscles: some evidence in support of a tendency to a slightly more prolonged period of muscular recovery in patients premedicated with chlorpromazine was established. (6) Unusual lethargy in the first postoperative hour was seen in 8 patients (6 of these had received chlorpromazine, 2 had had morphine for premedication). (7) Pulse rate: tachycardia was significantly more common in the chlorpromazine group before, during and after anaesthesia. (8) Blood pressure: no significant difference in the incidence of hypotension could be demonstrated. (9) Infusion of blood and dextran: patients in the chlorpromazine group received significantly more blood and dextran than those in the morphine group. (10) Postoperative nausea and vomiting occurred less often in patients premedicated with chlorpromazine. The difference was highly significant. (11) Postoperative analgesics were administered equally often to the 2 groups of patients. (12) Evidence of insufficient depth of anaesthesia (absence of total amnesia for the operation) was obtained in 13 patients, of whom 6 had been given chlorpromazine and 7 morphine. (13) Postoperative muscle pain caused by succinylcholine: the incidence was significantly reduced in the chlorpromazine group. (14) Local reaction to chlorpromazine, viz. slight tenderness of a week's duration, occurred only in one patient.

The results are discussed. It is concluded that the advantages in using chlorpromazine in pre-anaesthetic medication are a reduction in the incidence of postoperative nausea and vomiting and of the postoperative muscular pain caused by succinylcholine. These are outweighed by the disadvantage of reduced vasomotor control.—[Authors' summary.]

680. **The Cardiovascular Effects of Halothane in Normal Children**
M. MCGREGOR, H. T. DAVENPORT, W. JEGIER, P. SEKELJ, J. E. GIBBONS, and P. P. DEMERS. *British Journal of Anaesthesia* [*Brit. J. Anaesth.*] **30**, 398–408, Sept., 1958. 6 figs., 31 refs.

The cardiovascular effects of halothane anaesthesia were studied at the Children's Hospital, Montreal. In 28 children measurements were made of cardiac output, (by the dye method), blood pressure, and heart rate, and stroke output and peripheral resistance were calculated from these. The values obtained when the children were under halothane anaesthesia were compared with those obtained with nitrous oxide. It was found that the cardiac output decreased progressively with increasing concentrations of halothane. The reduction was 15% in Plane 2 (as judged clinically and electroencephalographically) and 23% in Plane 3. *Ronald Woolmer*

681. **Inhibitory Action of Halothane on Contractility of Human Pregnant Uterus**
M. P. EMBREY, W. J. GARRETT, and D. L. PRYER. *Lancet* [*Lancet*] **2**, 1093–1094, Nov. 22, 1958. 2 figs., 8 refs.

At the Nuffield Department of Obstetrics and Gynaecology, University of Oxford, the effect of halothane on the contractility of the human uterus was measured by external tocography in 12 patients. In 10 cases (9 admitted for surgical induction of labour and one for external version) records of painless contractions in late pregnancy were obtained, while in 2 cases (one of forceps delivery and one of caesarean section) the records were taken during labour; the difference between the contractions in these two groups is one of degree only.

After premedication with atropine (1/100th or 1/75th grain (0·65 or 0·86 mg.) only) the contractions were studied before induction with halothane in concentrations of between 2% and 3% in air enriched with oxygen, and again after recovery of consciousness. In all 12

cases halothane was shown to inhibit contractions, the effect appearing just after consciousness was lost—even in light planes of anaesthesia at which cervical dilatation produced respiratory stimulation—and disappearing with return of consciousness. A similar effect was also seen in one case with oxytocin-induced contractions. The authors suggest that, while not recommending the widespread use of halothane in obstetrics, this agent may be of special use in performing version or other intrauterine manipulation, in cases of " constriction ring ", or where impending tonic contractions may be threatening rupture of the uterus. *Raymond Vale*

682. **Vaporization of Halothane and Ether in the " Copper Kettle "**
S. A. FELDMAN and L. E. MORRIS. *Anesthesiology* [*Anesthesiology*] **19**, 650–655, Sept.–Oct., 1958. 5 figs., 5 refs.

The authors report from the University of Washington School of Medicine, Seattle, further experience with the " copper kettle " vaporizer introduced and described by the senior author some 6 years ago (Morris, *Anesthesiology*, 1952, **13**, 587). This inhaler was originally designed for chloroform, but is now largely used for ether. It is fitted with a vernier control and can be used for all liquid anaesthetic agents. Its use with ether and halothane is discussed; since the latter gas is very potent, exact control of the concentration is required. The vaporizer has a copper container, stands on a copper table top, and contains a sintered bronze vaporizing surface, which produces bubbles of small size, thus increasing the gas–liquid interface and so permitting maximum vaporization.

The ether vapour delivered by this machine was shown to correspond very closely with the standard vapour-pressure curve, while the halothane delivery was somewhat less exact. The necessary heat for vaporization is supplied from the surrounding air, copper being an excellent conductor. By means of the vernier very exact control is possible, but caution is necessary and dilution of the vapour is essential since lethal concentrations 10 to 20 times those required for anaesthesia can be produced in its absence. It is claimed that the precise control possible with this apparatus enables potent anaesthetics such as halothane to be administered safely. *W. Stanley Sykes*

683. **Suppression of Cyclopropane–Epinephrine Arrhythmias in Dogs by Four Phenothiazine Derivatives**
M. M. WINBURY, L. M. HAUSLER, J. K. WOLF, M. J. KLEIN, and W. M. GOVIER. *Anesthesiology* [*Anesthesiology*] **19**, 743–751, Nov.–Dec., 1958. 5 figs., 16 refs.

The authors describe a comparative study of the effectiveness of the 4 phenothiazine derivatives perphenazine, chlorpromazine, promazine, and mepazine in preventing arrhythmias due to adrenaline administered to dogs during cyclopropane anaesthesia. Perphenazine was the most active, and chlorpromazine and promazine the next most active, showing from 30 to 50% of the activity of perphenazine, whereas mepazine was much less effective, with a comparative effect of only 5 to 10%. These compounds also reversed the pressor action of adrenaline, but only when given in doses considerably higher than those required to protect the dogs against arrhythmias. *W. Stanley Sykes*

684. **Gas Analyzer for Rapid Estimation of Cyclopropane**
H. W. LINDE and H. L. PRICE. *Anesthesiology* [*Anesthesiology*] **19**, 757–761, Nov.–Dec., 1958. 1 fig., 1 ref.

Writing from the University of Pennsylvania, Philadelphia, the authors state that the " quick " gas analyser described by Scholander (*J. biol. Chem.*, 1942, **146**, 159) can be used for the rapid volumetric analysis of the concentration of cyclopropane during anaesthesia. Concentrated sulphuric acid will absorb cyclopropane, but it is destructive to rubber tubing; however, if the acid is diluted (100 ml. to 20 ml. of water) it is still effective and much less destructive. The gas is sampled with a 5-ml. syringe and injected into the analyser. Ethylene does not interfere with the analysis, but nitrous oxide and vinyl ether do. The method is not accurate for the estimation of ether concentration, but for cyclopropane it is accurate to within ±1%. *W. Stanley Sykes*

685. **Hepatotoxicity of Inhalation Anesthetic Drugs**
W. M. JONES, G. MARGOLIS, and C. R. STEPHEN. *Anesthesiology* [*Anesthesiology*] **19**, 715–723, Nov.–Dec., 1958. 6 figs., 11 refs.

In the interpretation of the toxic effects of anaesthetic agents on the liver the degree of anoxia, nutritional status, and changes in the hepatic blood flow are variables which are misleading, liver function tests lack accuracy and specificity, while inhalational methods lead to difficulties in determining the concentration of the agent to which the liver cells are exposed. For these reasons, then, the anaesthetic drugs used in these experiments on mice reported from Duke University, Durham, North Carolina, were given by mouth in measured doses and diluted with olive oil, a tuberculin syringe with a blunt, ball-ended, curved needle being used to pass the drug into the oesophagus. The authors state that by this method the liver can be exposed to much higher concentrations of drugs (without causing death of the animal) than when these are given by the respiratory route.

The agents tested, chloroform, halothane, trichlorethylene, vinyl ether, and ethyl ether, were given with the aim of determining the minimum narcotic and minimum lethal doses, the dose which produced threshold hepatotoxic effect, and the degree of liver injury associated with increasing concentrations of each drug. It was shown that these agents (given above in the order of decreasing anaesthetic potency) caused minimum hepatotoxicity in the same order. In regard to the minimum lethal dose the order was the same, except that chloroform and halothane were reversed, some animals surviving 100% " fluothane " (halothane). All the drugs could produce more or less liver damage, chloroform and vinyl ether causing the most severe damage, while ethyl ether was relatively innocuous. Halothane, while causing fatty infiltration, did not produce necrosis of the liver cells. *W. Stanley Sykes*

Radiology

686. **Effect of Combined X Rays and Ultrasonic Waves on the Development of Bean Shoots.** (Influenza dell'associazione radiazioni roentgen–onde ultrasonore nello sviluppo di germogli di fagiolo)
M. FACCINI. *Radioterapia, radiobiologia e fisica medica* [*Radioter. Radiobiol. Fis. med.*] **13**, 399–406, 1958. 1 fig.

Controlled experiments carried out at the University of Milan on the inhibition of the growth of bean shoots showed that a dose of 400 r. of x rays combined with ultrasonic waves (intensity of 1·5 watt per sq. cm. and frequency of 800 KHz) produced an effect comparable with that of 1,200 r. of x rays alone. Among the various possible mechanisms of this action a rise of temperature and chemical effects such as production of free radicals are not thought to be important factors. The author emphasizes the role of the pulsatile effect of ultrasonic waves on cellular particles, especially on cell membranes, which could act as a physical catalysis enhancing the effect of x rays by promoting the movement of molecules activated by the ionizing radiation. Clinical experiments using this method have been begun on experimental tumours and breast cancer.

J. Walter

RADIODIAGNOSIS

687. **A Contribution to the Encephalographic Diagnosis of Tumours of the Pineal Body.** (Beitrag zur pneumographischen Diagnostik der Epiphysentumoren)
E. KLAUS. *Acta radiologica* [*Acta radiol. (Stockh.)*] **50**, 12–17, July–Aug. [received Oct.], 1958. 2 figs., 15 refs.

The author claims that measurement of the distance between the posterior margin of the third ventricle and the cisterna ambiens, as seen in the lateral encephalogram, is of value in the diagnosis of tumours in the pineal region. Examination of a control series of 200 cases showed that this distance is normally 7 to 14 mm., whereas it is less than 6 mm. in cases of enlargement of the third ventricle and greater than 16 mm. in cases of pineal tumour.

A. Orley

688. **Dynamic Encephalography. A Report of Two Years' Experiences.** [In English]
E. PALMA, R. J. RODRÍGUEZ MARTÍNEZ, J. RODRÍGUEZ JUANOTENA, H. POLLERO, W. TAIBO, F. GOMEZ GOTUZZO, and W. PERILLO. *Acta radiologica* [*Acta radiol. (Stockh.)*] 27–33, July–Aug. [received Oct.], 1958. 3 figs., 24 refs.

The originality of the authors' method of encephalography consists in the use of cisternal puncture and of oxygen, which is less irritating and more easily absorbed than air, as the contrast medium. Moreover, exposures are made while the gas is still moving upwards and any excess of gas, cerebrospinal fluid, or both is allowed to escape through the needle. Because of these two factors they call their method "dynamic encephalography". The method may be used in most cases of increased intracranial pressure, but is contraindicated in the presence of severe cranial hypertension, particularly when there is danger of tentorial herniation. It is of most value in the diagnosis of lesions in the posterior fossa and of expanding lesions of the diencephalon, brain-stem, and hypophysis.

The technique, which is fully described, has been used in 135 cases with a transient mishap in one case only. In all the other cases the procedure was well tolerated and no serious accidents occurred.

A. Orley

689. **Encephalography with the Image Intensifier.** (Encephalographie am Bildwandler)
O. WIEDENMANN and K. H. LEUCHS. *Acta radiologica* [*Acta radiol. (Stockh.)*] **50**, 39–47, July–Aug. [received Oct.], 1958. 1 fig., 2 refs.

At the Neurological Clinic of the University of Munich the authors have made use of an image intensifier for the direct radioscopic observation of the filling process in the course of encephalography. Air is injected through a lumbar-puncture needle and its passage observed through the atlanto-occipital region and the base of the skull into the ventricles. The appearances in normal subjects and in various pathological conditions are described.

A. Orley

690. **Circumstances Surrounding Complications of Cerebral Angiography. Analysis of 546 Consecutive Cerebral Angiograms**
D. R. CODDON and H. P. KRIEGER. *American Journal of Medicine* [*Amer. J. Med.*] **25**, 580–589, Oct., 1958. 22 refs.

It is pointed out that some of the factors giving rise to complications of cerebral angiography have been defined, but that there are still differences of opinion concerning the contraindications to this procedure and the best technique of arteriography. For example, some workers consider that general anaesthesia prevents complications and obviates reactions related to vascular spasm, while others consider that it is the cause of complications. Similarly, while the risk of causing complications may be reduced by giving a limited number of small injections at considerable time-intervals, attempts to find a direct relationship between the incidence of complications and the rapidity and size of the injections have been unsuccessful.

In this paper from the Mount Sinai Hospital, New York, the authors present a study of 109 complications of cerebral angiography in 483 patients from whom a total of 546 angiograms were obtained. Two factors were associated with the occurrence of serious complications: (1) depression of consciousness at the time of arteriography, and (2) progression of neurological signs.

In this series no relationship was found between the cardiovascular and hypertensive state of the patient and the occurrence of a complication. There was a serious complication in one-quarter of the patients with aneurysm, but no apparent cause for this high incidence was found. Of the 109 complications, which are tabulated, 44 were innocuous and transient, 51 were serious but transient, and 14 were permanent. Of the permanent complications, 9 occurred in 8 patients who subsequently died, but the authors state that only in one case did death appear to be directly attributable to the procedure. Permanent non-fatal complications occurred in 4 (0·8%) of the patients.

The authors conclude that the value of arteriography must be considered in relation to the incidence and severity of complications. "In this series 80% of the arteriograms gave diagnostically useful information. Therefore, in consideration of the low rate of significant morbidity and the low rate of mortality . . . in selected cases cerebral arteriography provides diagnostic information which outweighs the risk of complication".

J. MacD. Holmes

691. **Radiological Observations on 33 Cases of Primary Interstitial Myocarditis during an Outbreak in the Haifa Area**

J. MUNK and K. T. LEDERER. *Journal of the Faculty of Radiologists* [*J. Fac. Radiol.*] **9**, 195–203, Oct., 1958. 8 figs., 23 refs.

Between May, 1956, and December, 1957, 61 cases of primary interstitial myocarditis in children from 6 months to 3½ years of age were seen in the Rambam Government and Rothschild Hospitals, Haifa, Israel. X-ray examination was carried out in 33 cases only, the remaining patients being *in extremis* or dead on admission. Of these 33, 22 died, necropsy being performed on 21.

The predominant radiobiological abnormality was generalized cardiac enlargement with passive pulmonary congestion, including, in some cases, lymphatic engorgement. There was a trace of pleural fluid in all except 5 cases, and cardiac pulsations were diminished on fluoroscopy in 16. Marked emphysema, which was probably due to concomitant diffuse interstitial pneumonia, a fairly common condition in Israel, was present in some cases. Discussing the differential diagnosis from interstitial pneumonia, the authors stress the importance of cardiac enlargement and Kerley's B lines in the diagnosis of myocarditis, and of emphysema of the periphery of the lungs in pneumonia.

D. E. Fletcher

692. **Third Ventricles of 12 mm. Width or More. A Preliminary Report.** [In English]

A. ENGESET and A. LÖNNUM. *Acta radiologica* [*Acta radiol. (Stockh.)*] **50**, 5–11, July–Aug. [received Oct.], 1958. 3 figs., 3 refs.

This report from the University Hospital and Clinic of Psychiatry, Oslo, is based on the study of 100 patients with cerebral atrophy (those with possible cerebral tumour or with increased intracranial tension being excluded) in whom encephalograms showed the third ventricle to measure 12 mm. or more in width and thus to be outside the normal limits of variation. In 98 cases there was also enlargement of the frontal horn. The methods used for measurement of the central parts of the ventricular system are described.

The patients (80 male, 20 female) were mostly between 45 and 70 years old, and the size of the third ventricle generally increased with age. However, it was between 12 and 15 mm. in 80 of the cases, and only in 3 was it 19 to 20 mm. wide. In 88 cases the patient had completely lost the capacity to work and in the remaining cases the working capacity was greatly reduced. Almost all the patients presented serious social problems, but psychic disturbance was the main cause of incapacity for work; many of the patients suffered also from a disturbance of the vegetative nervous and endocrine systems.

The authors consider that these findings confirm the assumption that in cases of cerebral atrophy the degree of enlargement of the third and lateral ventricles on encephalography can be correlated with the degree of disability.

A. Orley

693. **Barium Meal and Follow-through**

A. C. GLENDINNING. *Lancet* [*Lancet*] **2**, 664–667, Sept. 27, 1958. 2 figs., 8 refs.

Working in the Bromley (Kent) group of hospitals, the author has made an attempt to assess the significance of the radiographic finding of a gastric residue 6 hours after a barium meal, which since 1912 has been widely accepted as an indication of gastro-intestinal disorder with the result that a "barium meal and follow-through" is frequently requested by the physician as a routine. Starting in 1949, all patients undergoing barium-meal examinations were re-examined after one hour and a guess was made (in writing) as to whether or not there would be a significant residue (one-fifth to one-quarter of the meal) at 6 hours, when a further film was taken. The patient was first seen "fasting" [not defined] and took no food or drink until after the one-hour examination, a light lunch being permitted before the 6-hour film. [It is not stated whether or not the lunch was a standard meal provided by the hospital. The author is obviously aware of the difficulty or impossibility of assessing the size of a barium residue when the barium is mixed with food, but evidently does not consider that this invalidates his results.]

Altogether 1,000 examinations were carried out on 866 patients, of whom 215 were found to have a significant residue at 6 hours. In most cases the author's previous guess was found to have been correct, and he concludes that a practised observer should be able to forecast a 6-hour residue accurately "in more than 85% of cases". A comparison of the diagnoses in the group of patients with a 6-hour residue with those in the whole series showed that duodenal ulcer was proportionately considerably more frequent among the former, while the proportion of cases in which the findings (apart from delayed emptying) were normal was correspondingly less. These trends were similar for both males and females. No significant differences were observed in respect of other diagnoses.

It is therefore concluded that slow emptying of the stomach, as indicated by a residue of 20 to 25% of the meal at 6 hours, is frequently associated with duodenal disease. But since the probability of delay can usually be accurately predicted at the first examination, or at any rate at one hour, there is little advantage to be gained from re-examination at 6 hours. The barium follow-through examination is time-consuming and often unhelpful in the diagnosis of lesions elsewhere in the gastro-intestinal tract, particularly the large intestine, and should not be performed as a routine.

Denys Jennings

694. **The Intrahepatic Vasculogram and Hepatogram in Cirrhosis following Percutaneous Splenic Injection**
F. F. RUZICKA, E. G. BRADLEY, and L. M. ROUSSELOT. *Radiology* [*Radiology*] **71**, 175–186, Aug., 1958. 9 figs., 13 refs.

Abnormalities of the intrahepatic portal vasculogram in cirrhosis are described. The abnormality of the vasculogram is not related to function of the liver parenchyma as measured by liver-function tests. Rather it appears to be related to the pathologic anatomical changes produced by the disease process. An abnormal vasculogram may occur in a cirrhotic liver of any size but is more apt to occur in the small contracted liver. A cirrhotic patient with a normal vasculogram is more likely to have a large or "normal-sized" liver. The intrahepatic portal vasculogram is abnormal in approximately 71% of cases of cirrhosis. An abnormal vasculogram may be present when liver-function tests are normal and under such circumstances may be used as a sign supportive of the diagnosis of cirrhosis.

The hepatogram phase is largely dependent on the degree of portal vascularity and patency of vessels in a given area. The amount of opaque medium reaching liver sinusoids appears to play a major role in the density of the hepatogram. The pattern of the hepatogram is related significantly to the vasculogram. An abnormal hepatogram is likely to be found with an abnormal vasculogram, although other combinations occur. The usual abnormal pattern of the hepatogram in cirrhosis is a mottled radiolucency in an opaque background. Abnormal hepatogram patterns with intrahepatic lesions other than cirrhosis are briefly discussed.

No relationship was noted between density of the hepatogram and liver decompensation as measured by the usual liver-function tests, nor was any relationship observed between duration of the vasculogram and density of the hepatogram. In cirrhotic patients with a vasculogram of a duration longer than 10 seconds after the end of injection, there is a greater tendency to an abnormal hepatogram.—[From the authors' summary.]

695. **Roentgen Diagnosis of Acute Appendicitis**
C. SOTEROPOULOS and J. H. GILMORE. *Radiology* [*Radiology*] **71**, 246–256, Aug., 1958. 12 figs., 24 refs.

In a 3-year study of acute appendicitis, the possibility of accurate roentgen diagnosis has been proved, even in cases with vague and nonsuggestive symptoms. The x-ray findings are as follows: (1) Fluid level in the cecum best seen in the decubitus position, occasionally associated with small fluid levels in the terminal ileum. (2) Blurring of the distal portion of the right psoas muscle with secondary homolateral scoliosis of the lumbar spine. (3) Coarsening and edema of the mucosa of the cecum. Thickening of the wall of the cecum. (4) Localized ileus of the loops of the terminal ileum, with thickened septa between the loops of small bowel and the cecum. (5) Diffuse increased density over the region corresponding to the cecum and terminal ileum. (6) Flocculent gas densities in the area of the appendix. (7) Fecaliths of the appendix in the presence of suggestive clinical findings. (8) Widening and shortening of the extraperitoneal fat line.

A series of cases has been presented and analyzed. The importance of the decubitus position in the x-ray study of the abdomen is stressed.—[Authors' summary.]

696. **Achondroplasia of Pelvis and Lumbosacral Spine; Some Roentgenographic Features**
J. CAFFEY. *American Journal of Roentgenology, Radium Therapy, and Nuclear Medicine* [*Amer. J. Roentgenol.*] **80**, 449–457, Sept., 1958. 13 figs., 6 refs.

Writing from Columbia University and the Babies Hospital, New York, the author draws attention to certain features of achondroplasia which have not previously been stressed. The primary disorder of delayed cartilaginous growth and irregular endochondral bone formation is not confined to the extremities, but also affects other bones of cartilaginous origin in the same way. Thus in the pelvis impairment of growth is particularly observed in the iliac bones, so that the shape of the ossified portion of the ilium becomes somewhat squared in appearance. Persistence of cartilage is evident in the acetabular roof and in the triradiate cartilages, and the bony margins of the acetabula may therefore be represented as irregular horizontal lines, while the greater sciatic notch is flattened and is shown as a relatively deep and narrow cleft. The impairment of iliac development is more prominent in the vertical than in the transverse diameter, and thus may contribute considerably to the total loss of stature. Development of the centres for the greater and lesser trochanters of the femora may similarly be delayed. The sacrum shows narrowing in the transverse diameter and the sacro-iliac articulations are set abnormally deeply in the pelvis, so that the lower part of the lumbar spine may lie well below the iliac crests. In addition a marked lumbar lordosis is likely to be present as a result of the forward rotation of the sacrum on the malformed iliac bones. It is pointed out that the consequent prominence of the upper portion of the sacrum may subsequently interfere with pregnancy.

In the spine the ossification centres are also abnormally small and there is an absolute as well as a relative increase of cartilage. The vertical diameter of the intervertebral spaces may therefore be equal to that of the vertebral bodies, although in the normal child at 12 months of age this ratio is only 1:3. The dorsal aspects of the vertebral bodies are concave, particularly in the lumbar regions, instead of being straight or convex as in the normal spine. Impaired development of the anterior

aspects of the bodies may result in wedging and the development of " bullet-nosed " deformities which may simulate the abnormalities observed in cretins and gargoyles. Such deformities, particularly if localized to a single vertebra, may later be responsible for the development of a sharply-angled kyphos. The pedicles are also abnormally short, so that the spinal canal is flattened in its antero-posterior diameter. The transverse diameter of the lumbar vertebrae, in direct contrast to the normal, becomes progressively smaller in the distal portion of the lumbar spine, so that whereas in the normal lumbar spine the 5th lumbar body is by far the widest, in achondroplasia it is the narrowest. At the same time the interpedicular distances are progressively narrowed so that the spinal canal, instead of widening in the lower lumbar region, actually tapers. This abnormal narrowing renders achondroplasiacs peculiarly liable to symptoms of nerve-root compression from disk herniation and the development of osteophytes. *R. O. Murray*

697. **Pelvic Bones in Infantile Mongoloidism; Roentgenographic Features**
J. CAFFEY and S. ROSS. *American Journal of Roentgenology, Radium Therapy, and Nuclear Medicine* [*Amer. J. Roentgenol.*] **80**, 458–467, Sept., 1958. 14 figs., 2 refs.

In this communication from Columbia University, New York, the authors now supplement the findings presented in an earlier report (*Pediatrics*, 1956, **17**, 642; *Abstr. Wld Med.*, 1956, **20**, 401) which described characteristic and diagnostic changes in the pelvic bones of 18 mongoloid infants; they have now examined 48 such infants.

The cardinal features are: (1) reduction of the acetabular angle; this is measured by allowing the line of the acetabular roof to intersect a base line passing through both triradiate cartilages. (2) Reduction of the iliac angle, this angle being measured by allowing a line drawn along the lateral margin of the ilium to intersect the same base line. The average of the sum of these angles on both sides of the pelvis has been termed the iliac index. The amount of reduction of these angles and of the iliac index in their 48 cases in comparison with similar measurements in normal children was shown to be statistically significant, but contrary to the previous report (based on only 18 cases) no significant difference was now apparent between the sexes. Additional diagnostic features are the presence of severe bilateral coxa vara and hypoplasia of the ischial rami, which tend to taper abnormally as they approach the ischio-pubic junction.

The authors suggest that these deformities are associated with hypotonic musculature, and hope in a future study to correlate the changes described with muscular performance. Meanwhile the specificity of the appearance is stressed and it is emphasized that in the majority of cases a conclusive diagnosis can be made from inspection of the radiograph of the pelvis without recourse to measurements. Variations from the normal and the differential diagnosis from achondroplasia, the Ellis–van Crefeld syndrome, Hurler's syndrome, and Morquio's disease are considered in detail. A conclusive radiological diagnosis of mongolism may be made during infancy when the clinical diagnosis is still most uncertain. *R. O. Murray*

698. **Pyelographic Diagnosis of Lesions of the Renal Papillae and Calyces in Cases of Hematuria**
B. S. ABESHOUSE and J. O. SALIK. *American Journal of Roentgenology, Radium Therapy, and Nuclear Medicine* [*Amer. J. Roentgenol.*] **80**, 569–589, Oct., 1958. 15 figs.

The radiological diagnosis of the causes of haematuria of renal origin can be a most difficult problem, but recent improvements in technique have done much to eliminate diagnostic uncertainties. The authors of this paper from the Sinai Hospital, Baltimore, summarize the accepted pyelographic changes produced by such lesions as diffuse pyelonephritis, tuberculosis, and carcinoma, and add those produced by less well-known lesions such as " sponge kidney " or " congenital idiopathic dilatation of the collecting tubules ", necrotizing papillitis, and actinomycosis. A total of 39 distinct lesions are classified on a pathological basis into 9 main groups, the pathology of each lesion being briefly discussed and the helpful pyelographic changes mentioned.

Chronic focal pyelonephritis, where the disease is confined to a single papilla and calyx, is more common than is generally accepted, the condition in many cases " having been reported as focal, haemorrhagic, and necrotizing papillitis, solitary abscess, and carbuncle ". A difficult problem in differential diagnosis is the early erosive change at the tip of a papilla occurring in the caseo-cavernous type of tuberculosis, which may simulate or be confused with necrotizing papillitis, backflow, haemangioma, and papillary carcinoma. Other renal tumours, cysts, and " foam-cell " granuloma may also be confused with renal tuberculosis, which should never be diagnosed on radiological evidence alone. Renal infarction, which produces distortion of the pelvis and calyces and is often misdiagnosed as being due to other kidney diseases, also occurs more frequently than reports would indicate. Acute lymphatic and myeloid leukaemia may produce lesions extending into the pyramids, these appearing as filling defects in the minor calyces. *Michael C. Winter*

699. **A Safe Contrast Medium for Urethrography**
I. M. THOMPSON. *American Journal of Roentgenology, Radium Therapy, and Nuclear Medicine* [*Amer. J. Roentgenol.*] **80**, 627–630, Oct., 1958. 8 figs., 2 refs.

The ideal urethrographic contrast medium would be a non-toxic, homogeneous, water-soluble compound giving adequate radiodensity. Writing from the Department of Urology, University of Texas, Galveston, the author emphasizes that when an oily contrast medium is injected into the urethra there is a risk of oil embolism should extravasation of the medium into the surrounding vascular structures occur. A new medium, thickened sodium acetrizoate (" thixokon ") was used in approximately 200 cases, satisfactory urethrograms being obtained without any untoward local or systemic effects. The author states that urethrography is of considerable diagnostic help in many diseases of the lower urinary tract,

although inadequate technique may detract from its value. In the narrow urethra of children and in cases of urethral stricture urethroscopy is usually unsatisfactory, whereas a urethrogram may be very helpful. Other conditions in which urethrography is of value include urethral fistula, bladder-neck obstruction of various types, neurogenic bladder, para-urethral sinuses and ducts, and ectopic ureteral orifices.

Michael C. Winter

700. **Thixokon Cystourethrography**
J. F. GLENN. *American Journal of Roentgenology, Radium Therapy, and Nuclear Medicine* [*Amer. J. Roentgenol.*] **80**, 631–634, Oct., 1958. 1 fig., 8 refs.

In this paper from Duke Hospital and Duke University School of Medicine, Durham, North Carolina, the author describes the results obtained with a new contrast medium, " thixokon ", in over 60 cysto-urethrographic examinations. Thixokon is a solution of sodium acetrizoate thickened with a non-jelling starch consisting almost entirely of amylopectin; this thickening agent gives the medium a variable viscosity dependent on its state of motion, thus allowing easy introduction and also the desired retention of the medium within the urethra when injection ceases. The medium is water-soluble, highly radio-opaque (32% iodine content), and, according to the manufacturers, is non-toxic on intravenous and intraperitoneal injection into laboratory animals. The medium may lose radio-opacity if exposed to daylight for prolonged periods of time. Diagnostically satisfactory results were obtained in all cases without any untoward reactions or instances of extravasation.

Michael C. Winter

701. **Vasoseminal Vesiculography in Hypertrophy and Carcinoma of the Prostate.** [In English]
G. W. VESTBY. *Acta Radiologica* [*Acta radiol. (Stockh.)*] **50**, 273–284, Sept., 1958. 8 figs., 17 refs.

Vasoseminal vesiculography, that is, the radiographic visualization of the spermatic tract, was first described in 1913, and its use has subsequently been reported by several authors. Up to the present time, however, no systematic study of the contrast-filled ejaculatory ducts has been reported, and this paper describes such a study in 166 cases of hypertrophy and carcinoma of the prostate gland seen at Ullevål Hospital, Oslo, where vasectomy is performed on most prostatics. During this operation a cannula is inserted into the distal end of the cut vas deferens and some 10 to 12 ml. of 50% " nycotrast " is intermittently injected; during the injection several radiographs of the spermatic tract are taken. No grave complications have been noted.

The normal ejaculatory duct has a smooth, regular contour with several circular contraction rings along its length. In prostatic hypertrophy the ejaculatory duct usually retains its contraction rings and is smoothly dilated, the amount of dilatation appearing to be directly proportional to the degree of hypertrophy. The seminal vesicle and ampulla of the vas are usually also dilated. Of 126 cases of prostatic hypertrophy, 9 showed some irregularity of the ejaculatory duct in addition to the dilatation, and in these cases, although definite hypertrophy was present, co-existent carcinoma could not be excluded. Carcinoma of the prostate usually starts posteriorly in the region of the ejaculatory ducts; radiologically it is seen to cause marked unilateral or bilateral narrowing and irregularity of the ducts, with loss of the contraction rings, while later it extends to produce similar changes in the ampulla and the medial part of the seminal vesicle. Out of 32 cases of carcinoma (25 verified histologically and the remainder by rectal examination, presence of skeletal metastases, and elevated serum acid-phosphatase level) there was no demonstrable radiographic sign of carcinoma in 3. Simple inflammatory lesions may also cause changes in the spermatic tract, but here the ejaculatory duct is usually either spared or only mildly affected, and in only a few cases has the author experienced difficulties in differential diagnosis. He concludes that vasoseminal vesiculography establishes a definite diagnosis in approximately 90% of disorders of the prostate gland and should be performed in all cases in which vasectomy is carried out.

Michael C. Winter

RADIOTHERAPY

702. **Thyroid Neoplasms Following Irradiation**
G. M. WILSON, R. KILPATRICK, H. ECKERT, R. C. CURRAN, R. P. JEPSON, G. W. BLOMFIELD, and H. MILLER. *British Medical Journal* [*Brit. med. J.*] **2**, 929–934, Oct. 18, 1958. 6 figs., 13 refs.

This paper from the University of Sheffield and the Sheffield National Centre for Radiotherapy reports 7 cases of carcinoma and 2 of adenoma (described as " pre-malignant ") of the thyroid gland, in all of which the neck had previously been irradiated for the treatment of a benign condition. The pathological criteria for diagnosis are stated, and photographs of 2 of the patients (8 of whom were female) and photomicrographs of sections of the tumour in 3 cases are reproduced.

The initial condition was a benign naevus in 5 cases, thyrotoxicosis in 2, and eczema and keloid each in one. The estimated maximum dose of x rays or gamma radiation received by the thyroid varied from 130 r. to 2,700 r. The age at the time of first treatment was 2 to 5 months in 5 cases and varied between 12 and 26 years in the other 4. The intervals between irradiation and the first sign of goitre ranged from 5 to 37 years. The final histological diagnosis was of papillary or follicular carcinoma in 6 cases, anaplastic carcinoma in one, and adenoma in 2.

The evidence for a causal relationship between irradiation of the neck and the subsequent development of thyroid abnormality is discussed. It is noteworthy that the present series included 6 of the 12 cases of thyroid carcinoma developing before the age of 35 found in a review of the records of a number of hospitals in Sheffield since 1946. Moreover, in the 5 cases in which treatment was originally given for a localized skin lesion the initial appearance and maximum development of carcinoma occurred in that part of the thyroid underlying the area of greatest exposure to radiation. The authors conclude that exposure of the thyroid gland to ionizing radiation

in childhood predisposes to the subsequent development of neoplasm, but that the association of malignant change with irradiation in adult life is less certain.

[This paper provides the first support from Great Britain for the suggestion of American authors (such as Simpson and Hempelmann, *Cancer*, 1957, **10**, 42) that irradiation of the thymus of infants may predispose them to the later development of thyroid cancer. The objection that the abnormal thymus in such cases might itself be the cause of the later malignancy does not apply to the present authors' patients, who were irradiated for other conditions. There is at present no evidence that irradiation of the neck in adults can cause thyroid cancer —indeed, x-ray treatment of adult thyrotoxicosis appears to lead to an increase in the incidence of post-cricoid hypopharyngeal cancer, but *not* in that of thyroid cancer.]

K. E. Halnan

703. **X-ray Treatment of Frostbite.** (Рентгенотерапия отморожений)
V. N. Agafonova. *Вестник Рентгенологии и Радиологии* [*Vestn. Rentgenol. Radiol.*] **33**, 90–91, No. 5, Sept.–Oct., 1958.

The author reports the treatment with x rays of 30 cases of frostbite of the fingers and toes. The affected parts were cleaned up surgically before treatment, which was given as soon as practicable after the admission of the patient to the hospital. The technical details were as follows: 160 kV., 5 mA.; filter 0·5 mm. Cu.; half-value layer 1·1 mm. Cu.; focus–skin distance 30 cm.; fields 6×8 cm.; dose 120 r. per field. Two to 9 treatments were given at intervals of 1 to 2 days to a total dose of 240 to 1,080 r. In some cases local irradiation was supplemented by irradiation of the lower cervical or upper lumbar spine with a dose of 225 r. on 1 to 3 occasions at intervals of 4 to 5 days.

Pain might be temporarily exacerbated, but usually disappeared after 2 or 3 treatments, while circulation improved and swelling diminished. A demarcation line usually appeared about 10 days after the first irradiation, and separation of the necrosed tissue was usually complete after 15 days, though surgical intervention was sometimes required. Of the 30 patients treated, 26 were discharged with completely healed skin and the remaining 4 with small granulating wounds. *A. Orley*

704. **Contribution to the Study of the Effect of X Rays on Regeneration of Nerves.** (Contributo allo studio dell'azione dei raggi roentgen sulla rigenerazione dei nervi)
A. Gregori and A. Trenta. *Radioterapia, radiobiologia e fisica medica* [*Radioter. Radiobiol. Fis. med.*] **13**, 446–465, 1958. 9 figs., 12 refs.

Clinical experience having shown the beneficial influence of radiation on post-traumatic peripheral nerve lesions, experiments were therefore undertaken at the Radiological Institute of the University of Pavia on rabbits and guinea-pigs in which hemisection of the sciatic nerves was followed by x-irradiation, a dose of 60 r. at 180 kV. being given every 3 weeks to a total of 120 to 600 r. The chief effects observed in the irradiated nerves were an initial hyperaemia, capillary dilatation, and diapedesis followed by increased reabsorption and later vascular proliferation. Leucocytic immigration was increased and phagocytic activity enhanced. There was more rapid maturation of granulation tissue into fibrous tissue, but no appreciable change in the behaviour of nerve tissue itself or of cells in the sheath of Schwann.

J. Walter

705. **Radiation Therapy of Solitary Benign Cystic-appearing Lesions Involving the Long Bones of Children**
J. C. Cook, K. L. Krabbenhoft, and R. Songe. *American Journal of Roentgenology, Radium Therapy, and Nuclear Medicine* [*Amer. J. Roentgenol.*] **80**, 505–524, Sept., 1958. 16 figs., 42 refs.

Solitary, benign, cystic-appearing lesions involving the long bones of children may be classified according to the principal site of involvement as follows.

I. *Metaphysis* (A) Central: (1) solitary bone cyst; (2) monostotic fibrous dysplasia. (B) Eccentric: (1) aneurysmal bone cyst; (2) cyst of Sontag and Pile; (3) chondroma. II. *Diaphysis*: (1) solitary bone cyst; (2) monostotic fibrous dysplasia; (3) aneurysmal bone cyst; (4) chondroma or chondromyxoma. III. *Epiphysis*: (1) Codman's tumour; (2) giant-celled tumour of bone.

In the metaphysis by far the commonest type is the simple bone cyst in the region of the epiphysis. The response of these lesions to small doses of radiation suggests that they are of infective origin rather than true tumours. They appear to progress down the shaft with the growth of the bone and cause few symptoms unless a fracture occurs, as it does in nearly 50% of cases. Such fractures heal well. Response to irradiation may be taken as confirming the diagnosis, and biopsy is not essential except to exclude a malignant growth. Protracted irradiation with small doses produces an excellent response, with less deformity than could be expected after surgery. Aneurysmal bone cyst produces pain, swelling, tenderness, and limitation of movement, and may occur in flat bones and the spine as well as in the long bones. The honeycomb appearance is finer than the trabeculation seen in other types of cyst. In the diaphysis, apart from the rare chondroma, which is potentially malignant, all the conditions listed are benign and, apart from the aneurysmal bone cyst, asymptomatic. The rarest cause of a cystic lesion in children is the epiphysial chondromatous giant-celled tumour of Codman. These tumours occur at a younger age (12 to 20 years) than the typical giant-celled tumour, which occurs in the same location but almost always after closure of the epiphysial line.

In the authors' experience all of these solitary benign conditions respond similarly to radiotherapy, and biopsy is therefore justified only to exclude malignancy. While radiation cannot be used indiscriminately in children, particularly in the region of the metaphysis, careful application of small fractionated doses of radiation repeated at intervals to a tumour dose of 1,200 r. often produces excellent results. If after several weeks the desired result is not obtained, operation can still be carried out. With this dosage the growth of the bone continues normally. *I. G. Williams*